Introduction

Insulin receptor mutations lead to heterogeneous disorders; as severe as Donohue syndrome or as mild as “type A insulin resistance syndrome”. Patients with severe disorders are homozygous or compound heterozygous mutations. Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations. Homozygous insulin receptor gene mutations may rarely be responsible for mild type insulin resistance syndrome.

What is already known on this topic?

Insulin receptor mutations lead to heterogeneous disorders; as severe as Donohue syndrome or as mild as “type A insulin resistance syndrome”. Patients with severe disorders are homozygous or compound heterozygous mutations. Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations. Homozygous insulin receptor gene mutations may rarely be responsible for mild type insulin resistance syndrome.

What this study adds?

We emphasized that homozygous insulin receptor mutations may also cause mild clinical forms and we reported a novel homozygous mutation p.Leu260Arg on exon 3 on INSR gene in a patient with type A insulin resistance syndrome.

Abstract

Insulin receptor mutations lead to heterogeneous disorders; as severe as Donohue syndrome or as mild as “type A insulin resistance syndrome”. Patients with severe disorders are homozygous or compound heterozygous mutations. Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations, homozygous type mutations may rarely be responsible for this disease. We reported a novel homozygous mutation p.Leu260Arg on exon 3 on INSR gene in a patient with type A insulin resistance syndrome. In this article, we report an adolescent with type A insulin resistance syndrome due to a novel homozygous mutation on the INSR gene and detailed her medical follow-up. Different mutations in the INSR gene causes different phenotype and different inheritance pattern also, our report is important to making disease mechanism understand and also helping genetic counseling process.

Keywords: Hirsutism, Insulin resistance, Insulin receptor gene,

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Case Report

A 12-year-old girl was admitted to the pediatric endocrinology department for excess hair growing on her body. This complaint has been emerged over the last year. In the family history of the patient, her parents had no consanguinity and both parents were healthy. Her birth weight was normal and her past medical history was uneventful. She had a severe hirsutismus (Modified Ferriman-Gallwey Score was 30), acneiform rash on her face and severe acanthosis nigricans was observed in the axilla, neck and antecubital area (Figure 1A-1B). Her blood pressure was 110-70 mmHg. Her height was 156.5 cm (70th percentile), weight was 68.4 kg (99th percentile), and body mass index was 27.9 kg/m² (98th percentile) at the admission. Her puberty development was Tanner stage IV and her bone age was 13.5 years old. There was no history of spontaneous menarche. Laboratory examinations revealed that elevated fasting insulin level with normal fasting glucose.
Glycated hemoglobin level and oral glucose tolerance test results showed that she was in prediabetic state with marked hyperinsulinemia. Despite the severe hyperinsulinemia she had normal triglyceride, high-density lipoprotein (HDL) cholesterol and sex hormone binding globuline (SHBG) level and there was not hepatosteatosis on ultrasonographic evaluation. Her gonadotropin levels revealed that luteinizing hormone (LH) dominance with increased testosterone level. There was a polycystic ovary appearance on ultrasonographic evaluation. Her laboratory examinations results are detailed in table 1. Through the findings of clinical and laboratory examination type A insulin resistance syndrome was considered and INSR mutation analyses were planned. DNA Sanger Sequence analyses of the INSR all coding exons showed that a novel homozygous mutation NM_000208.4 c.779 T>G (p.Leu260Arg) in exon 3 (Figure 2). Genetic analysis of the parents demonstrated both were carrier of the same mutation. There were no clinical or biochemical hyperandrogenism and disorder of glucose metabolism on her mother, but her father was not detailed due to extenuating circumstances.

In her treatment first we started metformin (we increased the dose gradually at 2 gram/day) with life style modification. She could not do life style modification continuously during whole therapy process. After 1 year this therapy, we added oral contraceptive (OCP) (2 mg cyproterone acetate plus 35 microgram ethinyl estradiol) treatment because increasing hirsutism.

We aimed with this treatment procedure to suppress ovarian hyperandrogenism and to be benefited the anti-androgenic potential of cyproterone acetate. One year after treatment her hirsutism score markedly decreased (Figure 1C). Menarche occurred after this treatment.

During her clinical follow-up we added basal-bolus insulin regimen in her therapy because of marked hyperglycemia occurred after this treatment.

We reported a novel homozygous mutation p.Leu260Arg on exon 3 on INSR gene in a patient with type A insulin resistance syndrome. However, the mutation that makes the patient interesting is that it is homozygous. Because of different mutations in the INSR gene causes different phenotype and different inheritance pattern also, our report is important to making disease mechanism understand and also helping genetic counseling process. In conclusion, homozygous insulin receptor mutations rarely, as in our patient, might be associated with type A insulin resistance. 

Discussion
In adolescent period a patient with hyperandrogenism and severe insulin resistance whose findings could not been explained by other reasons such as obesity, should remind genetic insulin resistance syndromes to the clinicians. INSR gene mutations should be kept in mind in patients with severe insulin resistance but without metabolic dyslipidemia, low SHBG level and hepatosteatosis. There were many clues in clinical and laboratory features of our patient about the INSR mutation. Metabolic dyslipidemia (hypertriglyceridemia and low HDL-cholesterol levels) and steatohepatitis are closely associated with prevalent forms of insulin resistance (8). Key factor in the development of metabolic dyslipidemia and hepatic steatosis is postreceptor hepatic insulin resistance. Reduced liver fat synthesis plays a key role in the protection from dyslipidemia observed in patients with insulin receptoropathy (9). Eventually absence of metabolic dyslipidemia and fatty liver in a patient with severe insulin resistance like our patients is suggestive of a primary insulin receptor mutation.

There are no obvious genotype-phenotype correlations for INSR mutations. It has been suggested that the homozygous mutations of the α-subunit cause more severe clinical features, whereas heterozygous β-subunit mutations lead to milder forms (1,3). However, this is not the case in many patients. Many Type A insulin resistance patients with α-subunit mutations has been reported in our patients (5-7).

Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations however, homozygous type mutations may rarely be responsible for this disease. Nakashima N. et al. previously described a Japanese patient diagnosed as type A resistant insulin resistance syndrome with homozygous mutation (7). Later same mutation was detected in a patient from Morocco. Homozygous mutation was reported in 3 of 8 type A resistance syndrome patients in another series. Interestingly all Type A insulin resistance syndrome patients have α subunit mutations whose have homozygous mutation (6). We detected a novel homozygous mutation on exon 3 (p.Leu260Arg). Mutation that leucine instead of proline on the same codon was reported previously in a family. Homozygous form of this mutation (p.Leu260Pro) has been associated with leprechaunism (10). It was concluded that mutation is in this region which functionally links the insulin binding site on the α-subunit with the tyrosine kinase domain on the β subunit (10).

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Currently available therapies of genetic insulin resistance syndromes are nonspecific. Dietary changes and exercise in addition to drug therapy (metformin with or without insulin) have been mainstay the reduce the insulin resistance (8). Commonly, patient with mild INSR defects present peripubertally as oligomenorrhea and hyperandrogenism with acanthosis nigricans and sometimes misdiagnosed as polycystic ovary syndrome (11). At presentation, diabetic hyperglycemia has often yet to develop as our patient (8). Hirsutism treatment is difficult in these cases, but we have received good response to cyproterone acetate treatment (11).

We detected a novel homozygous mutation p.Leu260Arg on exon 3 on INSR gene in a patient with type A insulin resistance syndrome. However, the mutation that makes the patient interesting is that it is homozygous. Because of different mutations in the INSR gene causes different phenotype and different inheritance pattern also, our report is important to making disease mechanism understand and also helping genetic counseling process. In conclusion, homozygous insulin receptor mutations rarely, as in our patient, might be associated with type A insulin resistance.
Table 1. Laboratory data of a patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result (Normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>74 mg/dl</td>
</tr>
<tr>
<td>Insulin</td>
<td>217 mIU/ml (N&lt;20)</td>
</tr>
<tr>
<td>Glycohemoglobin</td>
<td>%5.74</td>
</tr>
<tr>
<td>OGTT 120 minute glucose</td>
<td>162 mg/dl</td>
</tr>
<tr>
<td>OGTT 120 minute insulin</td>
<td>893.5 mIU/ml</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>59 mg/dl</td>
</tr>
<tr>
<td>High-Density Lipoprotein-cholesterol</td>
<td>71 mg/dl</td>
</tr>
<tr>
<td>Total-cholesterol</td>
<td>144 mg/dl</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>15/15 IU/l</td>
</tr>
<tr>
<td>FSH</td>
<td>6.5 mIU/ml</td>
</tr>
<tr>
<td>LH</td>
<td>14.4 mIU/ml</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>190 ng/dl (N&lt;55)</td>
</tr>
<tr>
<td>DHEA-SO4</td>
<td>104 mcg/dl (N&lt;350)</td>
</tr>
<tr>
<td>SHBG</td>
<td>92.07 nmol/l (N: 17-155)</td>
</tr>
</tbody>
</table>

*OGTT; oral glucose tolerance test, ALT; alanine aminotransferase, AST; aspartate aminotransferase, FSH; follicle-stimulating hormone, LH; luteinizing hormone, DHEA-SO4; dehydroepiandrosterone sulphate, Sex hormone binding globuline (SHBG)
**Figure 1.** Clinical features of patient. A. severe acanthosis nigricans. B. Hirsutism before and treatment and C. after treatment

**Figure 2.** DNA Sequencing Chromatogram of the patient. Arrow showed homozygous NM_000208.4 c.779 T>G (p.Leu260Arg) mutation in the exon 3 of INSR Gene