A rare case of Syndromic diabetes due to an INSR pathogenic variant

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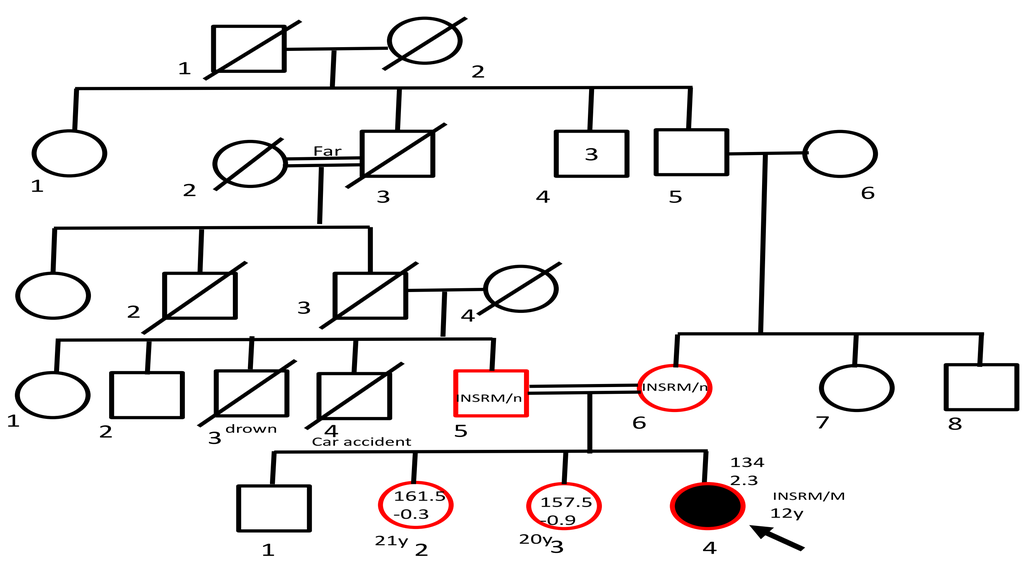
History

A 12-year-old girl , was referred after being diagnosed with diabetes and severe diabetic ketoacidosis.

Past history; bilateral oophorectomy at the age of 63 days. This was due to the presence of bilateral multiple ovarian cysts, diagnosed at the time as Juvenile Granulosa cell tumor.

Family history; consanguineous parents (1st cousin), no history of diabetes or similar condition



Examination

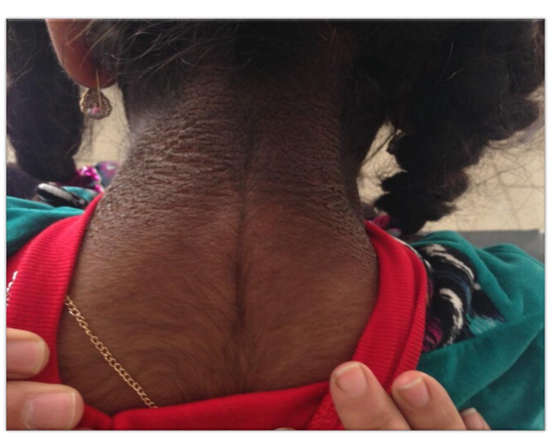
Examination; hypertrichosis, coarse facial features, high arched palate, overcrowded teeth. Acanthosis nigricans on the neck, axilla, and site of previous laparotomy operation

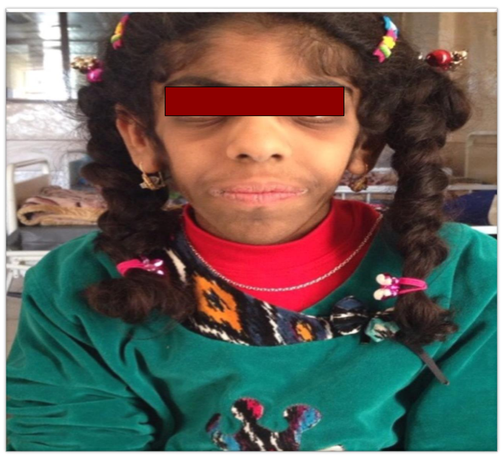
Height 134 cm /-2.3 SD)

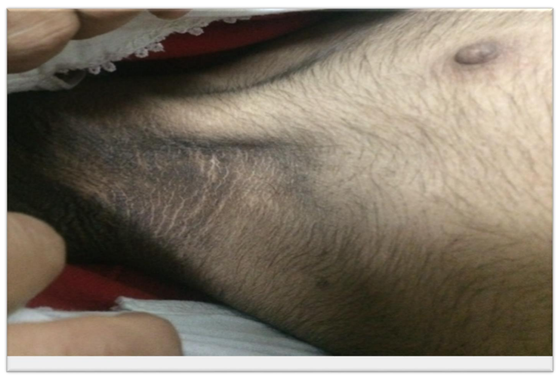
Weight; 30 kg

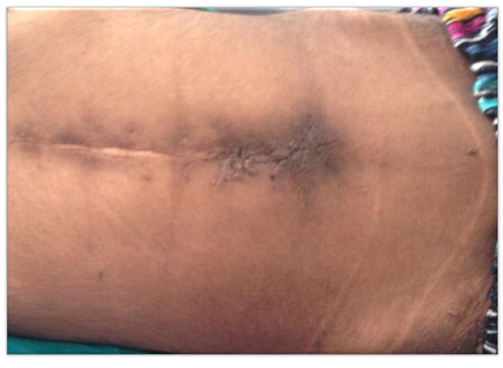
Tanner staging was B1P2A1

Her psychomotor development was normal









Investigation

Her initial investigations showed insulin resistant diabetes and growth hormone deficiency:

C peptide; 12.54 ng/ml , 8.68 ng/dl (n: 1.1-4.4 ng/ml)

Insulin; >1000uUml (2.6-24.9) (During hospital admission for DKA)

ACTH: 31.64 pg/ml. (n: 7.7-63.6pg/ml)

Cortisol: 788.4 nmol/L (n: 64-327 mmol/L) (stress)

IGF1; 65.37 ng/L (< -3 SD)

FSH; 80 mIU/ml

LH ; 11.58 mIu/ml

Estradiol; <10 pg/ml

Follow up

At the age of 13.9 years she was 139.5 cm (-3.1 SD) and her bone age was 10 years. Growth hormone stimulation was done with Insulin; Peek GH level reached 3.78 ng/ml, cortisol level of that sample was 278.7 nmol/l (she didn't develop hypoglycemia during the test).

Her growth velocity was 4 cm/year. She was put on growth hormone and sex steroid replacement therapy.

She is on total daily dose of 84 U insulin (2.6 U/kg) and her HbA1c is 10%. Metformin in dose of 850 mg twice daily recently been added with some minor improvement in her HbA1C (9.6%)

Genetic testing

Whole Exome Sequencing (WES) was carried out. Detected variants were filtered using bioinformatic software (Ingenuity and Varaft). She was found to be homozygous for a known pathogenic variant *p.Thr937Met (c.2810C>T*) in the *INSR* gene causing Rabson–Mendenhall syndrome her parents tested heterozygous for the same variant.

Conclusion

The incidence of Rabson–Mendenhall syndrome is estimated to be less than 1 in a million people. Insulin resistant diabetes mellitus, short stature, dysmorphic features, multiple ovarian cysts and hypogonadotropic hypogonadism have been described in these patients. In our case, the patient has hypergonadotropic hypogonadism due to a bilateral oophorectomy which may not have been indicated. Genetic testing in such cases of complicated diabetes with other phenotypic features could facilitate appropriate diagnosis and treatment.

All pictures were published with parents' permission.

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