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A Novel Mutation of INSR Gene in a Child with Type A Insulin Resistance

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Background

- ❑ Mutations of insulin receptor gene (INSR) lead to a wide spectrum of inherited insulin resistance syndromes.
- ❑ Type A insulin resistance is one of the these syndromes which is inherited autosomal dominant and leads to mild clinical symptoms after puberty (1).

Objective

- ❑ To report a novel mutation of *INSR* gene mutation in a case of Type A insulin resistance who presented with transient neonatal diabetes and then episodes of hypoglycaemia and hyperglycaemia during childhood.

Case:

- ❑ Full-term Afro-Caribbean female infant, of birth weight 1.89 kg, developed transient neonatal diabetes with negative genetic testing (microarray, TNDM 6q methylation analysis).
- ❑ At the age of 2.8 years, she presented with episodes of postprandial and fasting hypoglycaemia. Her examination showed satisfactory growth, lipodystrophy, acanthosis nigricans and isolated thelarche.
- ❑ Investigations demonstrated that the child after 12 hours of fasting developed hypoglycaemia (glucose 2.8 mmol/L), with inappropriately raised insulin level of 5.4 mU/L.
- ❑ Her oral glucose tolerance test (OGTT) (Table 1) showed excessively high levels of insulin throughout the test (>300 mU/L) along with hypoglycaemia (glucose 1.6 mmol/L) at 2.5 hours of the test. She had dietary modification with some improvement in hypoglycaemia.
- ❑ She continued to have postprandial hypoglycaemia and was started on Acarbose 12.5mg TDS (upto 25mg TDS) at the age of 5 years.
- ❑ She had negative genetic analysis for Familial Lipodystrophy (*LMNA* and *PPARG* genes) and Hyperinsulinism (*ABCC8* and *KCNJ11* genes).
- ❑ She was stabilized on acarbose treatment (upto 25mg TDS) for the management of PPHH that lasted for 2.5 years.
- ❑ Subsequently, she developed intermittent episodes of hyperglycaemia along with postprandial and fasting episodes of hypoglycaemia recorded persistently on continuous glucose monitoring.
- ❑ HbA1c and fasting lipids remained within the normal range.
- ❑ Suppressed androgens and pelvic ultrasound with pre-pubertal appearance of her internal genitalia until the age of 8.7 years.
- ❑ Normal baseline pituitary function.
- ❑ LHRH showed predominant FSH response.
- ❑ Treatment of metformin along with carbohydrate diet modification and corn starch started at the age of 7 years not only improved fasting tolerance but also episodes of hyperglycaemia and post-prandial hypoglycaemia.
- ❑ Genetic testing identified a novel heterozygous deletion of exon 22 in INSR gene.

Table 1: Oral Glucose Tolerance test (OGTT)

Age: 2 years and 8 months

Time (Min)	0	30	60	90	120	150
Blood glucose (mmol/L)	3.7	9.2	11.9	6.5	5.7	1.6
Insulin (mU/L)	19.9	>300	>300	>300	>300	225

Age: 4 years

Time (Min)	0	30	60	90	120	150
Blood glucose (mmol/L)	3.2	8.4	6.4	6.1	4.3	2.4
Insulin (mU/L)	7.5	>300	>300	>300	240	127

Conclusion:

- ❑ The present case details the clinical features of a patient with genetically proven Type A insulin resistance.
- ❑ The major features of this condition usually becoming clinically apparent in adolescence (2).
- ❑ Early age manifestation, neonatal diabetes and also PPHH can be another presentation of this disease.
- ❑ The remarkable point of the current case report is early different clinical presentation of Type A-IR with a novel INSR mutation that illustrates a range of different glycaemic presentations, and how IR can masquerade as other disorders.
- ❑ Children with this can be quite challenging to manage using pharmacotherapy and dietary modification (3).
- ❑ Further accumulation of genetically proven cases and long-term treatment outcomes following early diagnosis are required to understand the dynamics of this disease.

References

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