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A REVIEW ON RARE GENETIC INSULIN RESISTANCE DISORDER: LEPRECHAUNISM / DONOHUE SYNDROME

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ABSTRACT

Insulin resistance caused by rare genetic conditions are the group of inherited metabolic disorders that are characterized by the fact that the body does not respond to insulin properly although there are normal or very high levels of insulin in the blood. These disorders are mainly caused by mutations in the insulin receptor or in the signalling molecules that are involved after the receptor and they are accompanied by severe metabolic complications. Leprechaunism or Donohue syndrome is the most extreme phenotype in this group of disorders and it is significantly due to homozygous or compound heterozygous mutations in the INSR gene. Affected Patients mostly represents with intrauterine growth retardation (IUGR), dysmorphic features, severe hyperinsulinemia, multi-organ involvement in the neonatal period and there is a high mortality rate during the first few years of life. This review mainly focuses on classification, molecular genetics, and clinical manifestations of rare genetic insulin resistance disorders, particularly Leprechaunism. Diagnostic approaches, management strategies in vogue, and emerging therapies are also discussed. The understanding of these rare disorders will not only assist in early diagnosis, proper genetic counselling, and targeted therapy but will also grant new insights into the disease mechanisms. Furthermore, Research is required to enhance the clinical outcomes and quality of life in the affected patients.

KEYWORDS: Insulin resistance; Genetic metabolic disorders; Leprechaunism; Donohue syndrome; Insulin receptor mutation; Hyperinsulinemia; Growth retardation; Rare diseases; INSR gene; Endocrine disorders.

INTRODUCTION

A metabolic condition known as insulin resistance refers to where the liver, skeletal muscle, and the adipose tissue; the insulin-sensitive tissues do not properly respond to the circulating insulin, thus resulting in less glucose being absorbed or utilized.[1] Traditionally, the metabolic activity of the human body involves insulin modulation as the main actor in the metabolism of carbohydrates, lipids, and proteins and at the same time influencing the growth and even differentiation of cells.[2] Therefore, any disturbance in insulin action would have metabolic ramifications all over the spectrum.[3] Insulin resistance is however closely associated with obesity, metabolic syndrome, and type 2 diabetes, while a small but very important group of patients with insulin resistance caused by genetic mutations falls outside the typical classifications.[2,4] Genetic insulin resistance disorders are rare and not common but rather possess similarities with the metabolic disorders of different nature types such as early onset, extreme hyperinsulinemia, and severe metabolic instability being the main symptoms of all these disorders.[5] The course of acquiring insulin resistance is totally different from that of genetic insulin resistance as the latter is completely not associated with lifestyle factors and its symptoms may sometimes start showing during pregnancy or at the newborn stage or also in infants upto the age of 1 year.[3,6]

Typical symptoms of these patients include

- Retarded Growth,
- Delay In or Abnormal Development of Facial Features,
- Skin Problems, and
- Hormonal Production Problems, Among Others.[7]

The more severe the symptoms are, the more the signalling cascade of insulin is disrupted.[8] For these

conditions, children are frequently ignored, misdiagnosed, or provided with late necessary treatment due to their rarity and variability of symptoms.[9]

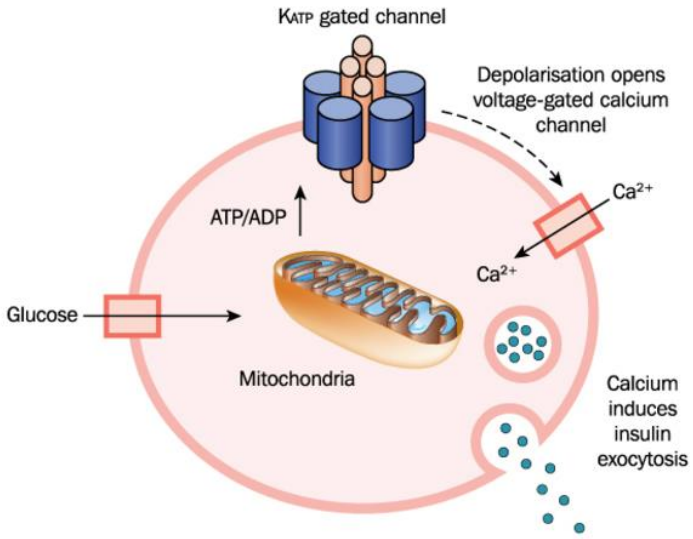

Figure 1.1: Leprechaunism (or) Donohue Syndrome.

Insulin resistance at the molecular level has mechanisms that either target the insulin receptor or the insulin post-receptor intracellular signalling cascades.[10] The insulin receptor, for instance, is a hetero-tetrameric glycoprotein that has the unique quality of being a transmembrane protein with a built-in tyrosine kinase activity. The receptor is able to perform its role in the downstream metabolic and mitogenic signalling by the activation of its intrinsic tyrosine kinase activity.[3, 11]

Mutations in the insulin receptor gene (INSR) can either lowers the insulin binding or cause the receptor processing or the membrane expression or the signal transduction to be ineffective.[12] Consequently, because of excess receptor dysfunction, pancreatic β-cells release more insulin than they normally would, which causes the threshold of hyperinsulinemia to be greatly surpassed.[13]

Chronic hyperinsulinemia is responsible for the secondary clinical manifestations like acanthosis nigricans, ovarian hyperandrogenism, and abnormal somatic growth, etc. that are seen in such cases; it is a causative factor for these manifestations rather than a consequence.[1,14]

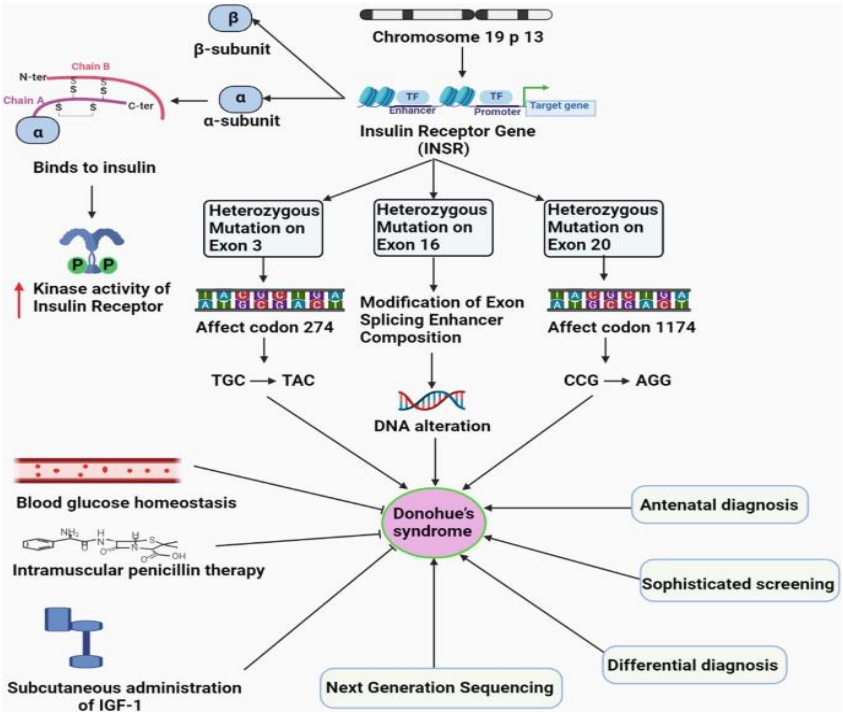

Figure 1.2: An Overview of Leprechaunism.

Genetic insulin resistance syndromes are rare and generally classified into three types based on the age of the patient at the onset of the clinical symptoms, their degree of severity and the type of genetic defect.[15] namely:

1. Type A insulin resistance syndrome,
2. Rabson-Mendenhall syndrome and
3. Leprechaunism

Type A insulin resistance syndrome usually occurs during puberty or young adulthood and typically comes with symptoms such as hyperandrogenism and acanthosis nigricans being the most common.[16]

The Rabson-Mendenhall syndrome corresponds to the mildest case of insulin-resistant phenotype characterized by retardation of growth, coarse features of the face, dental abnormalities, and the occurrence of diabetes mellitus at an early age.[17]

Leprechaunism or Donohue syndrome is the condition that is most severe along the spectrum of insulin resistance and hence it is usually associated with almost total loss of the functionality of insulin receptors.[8, 18]

Leprechaunism is an extremely rare genetic disorder characterized by the autosomal recessive trait and by the loss-of-function mutations in the INSR gene either through homozygous or compound heterozygous mechanisms.[19]

The first description of the disorder was in the mid-20th century when babies with unique facial features and conditions were severely retarded during the pregnancy and after birth and had wide-ranging metabolic problems.[20] The word "leprechaunism" came from the typical elves-like facial appearance seen in the infants affected by the disorder but it is now more correctly called Donohue syndrome which is a term that does not carry any negative undertones.[1]

Clinical Presentations

The clinical presentation of Leprechaunism can be listed as follows:

- Intrauterine growth retardation,
- Complete absence of subcutaneous fat,
- Excessive hair on the body,
- Thickened skin at some places,
- Enlarged genitalia, and
- Ears with abnormal development.[5,11]

Extreme insulin resistance leads the patient to a cycle of fasting hypoglycemia and postprandial hyperglycaemia, a sort of internal battle of the body's inability to regulate glucose.[3] Other hormonal disorders may include enhanced levels of male hormones, early maturation of bones, and heart muscle disease.[7] Affected areas of multiple systems make the importance of insulin signalling for normal growth and development very clear.[11]

The prognosis for Leprechaunism is extremely poor, and most infants die within the first few years because of various complications related to metabolic decompensation, recurrent infection, or organ failure.[2] The diagnostic approach is facilitated by the recognition of classic clinical features, the demonstration of exceptionally high insulin levels, and confirmation by molecular genetic testing of the INSR gene.[4]

However, genetic counselling is clave since prenatal diagnosis is available in families already aware of the specific mutations.[12] Due to the extreme rarity of Leprechaunism, data mainly consist of single case reports and very few case studies. Thus, the treatment protocols have not been comprehensively elaborated.[19] Nevertheless, the correct timing of diagnosis is the most important factor that would lead to the metabolic stabilization process, provision of timely information, and good decision-making in the affected families.[10]

Diagnostic Algorithm for Suspected Donohue Syndrome[4,7,15]

Neonate / Infant Presenting With:

- Severe IUGR
- Dysmorphic Facial Features
- Lack of Subcutaneous Fat
- Abnormal Glucose Fluctuations

↓

Serum Insulin Measurement

↓

Marked Hyperinsulinemia Detected

↓

Exclude Secondary Causes of Insulin Resistance

↓

Molecular Genetic Testing (INSR Gene Sequencing)

↓

Biallelic INSR Mutation Identified

↓

Confirmed Diagnosis: Donohue Syndrome

↓

- Genetic Counselling
- Carrier Testing
- Prenatal Diagnosis in Future Pregnancies

DISCUSSION

Rare genetic insulin resistance disorders represent some of the most biologically informative yet clinically challenging conditions in endocrinology. Among them, Leprechaunism, more appropriately termed Donohue syndrome, reflects the most profound disruption of insulin receptor function and provides a unique human model of near-complete insulin receptor inactivity. In contrast to the common insulin resistance mechanism in obesity or type 2 diabetes, leprechaunism is due to inherent structural/functional abnormalities of the insulin receptor, which results in the impairment of the following signalling pathways, as they are vital for glucose metabolism, growth, & cell differentiation. The hyperinsulinemia observed in the affected infants indicates a compensatory mechanism of pancreatic β-cell

hyperplasia. However, despite the significantly high levels of insulin in the circulation, the peripheral tissues are still unable to utilize glucose properly. This paradoxical situation explains the typical episodic presentation of fasting hypoglycemia and postprandial hyperglycemia. The chronic hyperinsulinemia also plays a role in the secondary endocrinopathies, such as hyperandrogenism and ectopic growth abnormalities in some organs, which emphasize the dual role of insulin as a metabolic and mitogenic regulator. The multi-organ involvement in the Donohue syndrome also emphasizes the physiological importance of insulin signaling in the body, which goes beyond the regulation of glucose metabolism. The intrauterine growth restriction, lack of subcutaneous fat, and dysmorphic features also indicate the impairment of anabolic signalling pathways during foetal development. Cardiac hypertrophy, renal abnormalities, and increased susceptibility to infections further add to the clinical problems and aggravate the prognosis.

The associated high mortality rate in early infancy is thought to result from metabolic instability, infections, and the progressive failure of vital organs. From the diagnostic point of view, it is crucial to have an early index of suspicion. The presence of severe growth retardation, distinctive facial features, marked hyperinsulinemia, and absence of obesity should raise the possibility of genetic insulin receptor defects. Molecular genetic analysis for the presence of biallelic mutations in the INSR gene not only confirms the diagnosis but also allows for precise genetic counseling. Prenatal diagnosis and carrier detection assume greater significance in consanguineous populations or in families with previous affected siblings. From a therapeutic standpoint, the approach is largely supportive, with the primary aim of stabilizing glucose levels and attending to nutritional requirements. Standard insulin therapy is generally ineffective because of receptor-mediated resistance. Recombinant insulin-like growth factor-1 (IGF-1) has been investigated as an alternative strategy to bypass the defective insulin signaling pathway, with variable but generally poor success. Although these approaches may offer temporary benefits in terms of metabolic control, they have not impacted survival rates. However, recent advances in molecular genetics have enhanced the diagnostic specificity, but specific therapies directed at the defect in the receptor have yet to be developed. Future research in receptor chaperones, gene therapy, or new signaling modulators may provide new hope for therapeutic intervention. In addition, the study of such rare conditions may provide important insights into the biology of the insulin receptor, which may potentially be used in the development of therapies for more common metabolic disorders. Finally, there is a need for further research to enhance the outcome of this catastrophic disease.

CONCLUSION

Rare genetic insulin resistance disorders are extreme cases of inheritance that are difficult but sometimes impossible to manage and that reveal important things about the insulin signalling and the metabolic controls. Leprechaunism, being the harshest form, is characterized by very high insulin resistance, the typical clinical signs, and early death. Genetic testing has made a great impact on the diagnosis as it has become more precise; better understanding of the disease mechanisms has been made possible. Nonetheless, the treatment remains limited and mainly supportive. Clinical research aimed at molecular-targeted therapy and preventive strategies might result in better health for the concerned population. The health professionals' heightened sensitivity is the essential prerequisite for speedy identification, most appropriate treatment, and timely genetic counselling.

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