UNIVERSITY OF CAMBRIDGE

Peterborough and Stamford Hospitals NHS Foundation Trust

Acid Labile Subunit Deficiency

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Introduction

Acid labile subunit (ALS) protein in a glycoprotein which is exclusively produced in liver and secreted into the circulation.

ALS protein plays a vital role in maintaining the serum insulin-like growth factor (IGF-1) by prolonging the half-life of IGF-IGFBP3/IGFBP-5 binary complexes.

ALS deficiency due to IGFALS gene mutation results in primary IGF-1 deficiency and associated with growth impairment, insulin resistance and occasionally delayed puberty.

Animal studies show that genetic targeted ablation of IGFALS gene appeared to increase the insulin sensitivity. However the pathophysiological mechanisms for this association are only partially understood.

Despite profound IGF-1 deficiency, the impact on postnatal growth is minimal.

Case report

9 years old boy was referred for short stature (Height -1.8 SDS and Weight -1.8 SDS). He is the sixth of non-consanguineous parents of asian origin. His birth weight was 2.9 kg (-1.3 SDS). He had no dysmorphic features.

His older sister (18 years) was diagnosed with Idiopathic short stature with final adult height of -3.9 SDS. His mother's height 160cm (-0.6 SDS) and father's height 174 cm (-0.6 SDS) and his mid-parental height 170.5cm (-0.8 SDS). There was strong family history of type 2 diabetes.

At 12 years of age, He became overweight and had developed marked acanthosis nigricans. BMI 22.56 (91-98TH centile).

At 13.8 years, Pubertal assessment showed pubic hair Tanner stage 1, genital stage 2 testicular volume 6ml bilaterally. Despite pubertal progression, his height velocity remained at 5.3 cm/year (-1.7 SDS).

Investigations

Persistently low IGF-1 levels (<3.3 nmol/L, Normal Range: 8.5 – 60)

Coeliac screen was negative.

Thyroid function test was normal.

Bone age was equivalent to his chronological age at 9 yr.

Insulin Tolerance Test on two occasions failed to induce hypoglycaemia.

Glucagon stimulation test showed normal GH peak (8 ng/L)

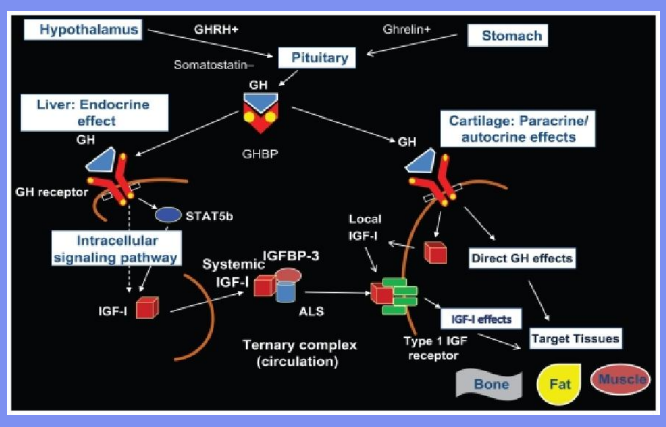
LHRH test showed pubertal response at 13.8 years.

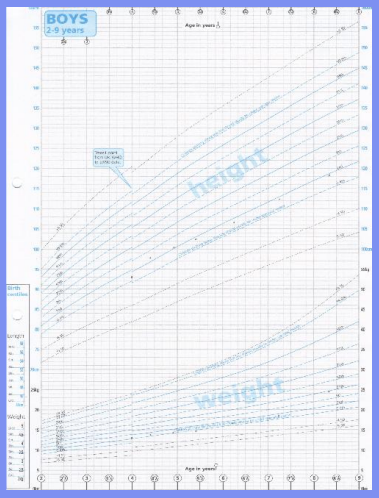
Oral Glucose Tolerance Test (OGTT) was found to be normal with insulin resistance (HOMA-IR 19.9) and subsequent OGTT showed impaired glucose tolerance.

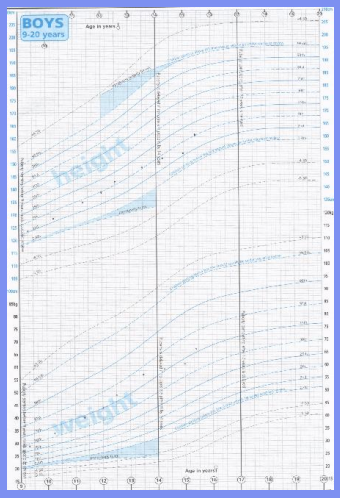
Leptin and Adiponectin levels were not suggestive of insulin receptor mutation.

Lipid profile was normal.

Whole Exome Sequence identified missense mutation in exon 2 of IGFALS gene (IGFALS p.Ala155Glu).







Phenotypic and Biochemical features of ALS deficiency

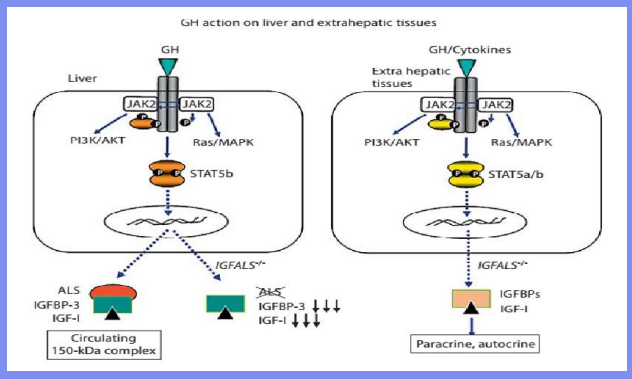
Mild to moderate growth failure despite severe IGF-1 deficiency and this can be attributed to preservation of local IGF-1 production secondary to elevated GH secretion.

Insulin Resistance – characterised by normal fasting glucose and high insulin levels.

Delayed puberty – reported in half of the male cases.

Significantly low levels of IGF-1 and IGFBP-3 – thought to occur as a result of increased turnover rather than decreased synthesis.

Reduced Bone Mineral Density has been reported but its not a consistent feature.



Conclusion

ALS deficiency is a rare condition and it is associated with short stature and insulin resistance.

Insulin insensitivity may be due to increased GH, impairing insulin action by lipolytic effect or due to low IGF-1 level which has sensitizing role in glucose update by muscles.

Despite the marked reduction in IGF-1, the growth impairment can be mild to moderate. The preserved expression of locally produced IGF-1 might be responsible for the preservation of linear growth near normal.

The current knowledge of biological role of ALS on foetal growth and pubertal growth is sparse and needs further research to understand the effect of ALS on prenatal growth.

Response to GH therapy was poor in ALS deficiency. However it is reported in literature that a child with Heterozygous mutation for IGFALS gene had good response to GH therapy. Poor response to GH therapy has been reported for homozygous mutations. Needs more research to explore the treatment options including GH, rhIGF-1 or both.

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