A patient with a novel homozygous mutation in IGF1-R gene and response to growth hormone therapy

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ABSTRACT

Background: fetal growth is affected by multiple factor. One of the major factors is IGF-1 which also have a role in post-natal growth and the development of fetal brain, inner ear and retina.

Subject: A 9.5-years-old boy born to healthy consanguineous couple presents with severe pre and post-natal growth failure, dysmorphisim , developmental delay and visual impairment.

Methods: auxological, hormonal and molecular genetic profiles was reviewed and the effect of growth hormone therapy on his linear growth discussed.

Conclusion: The reported case represent the complicated role that IGF1 play in the human linear growth, brain and eye development.

INTRODUCTION

There are multiple factors affecting fetal growth, including maternal, fetal, placental and other environmental factors. Insulin like growth factor-1 (IGF-1) has a major role in promoting fetal and post-natal growth. It is also proven that IGF1 promotes brain, inner ear and retinal development.(1–5)

CASE REPORT

We report a 9 years old boy born at 31 weeks of gestation to a consanguineous parents by cesarean section because of severe oligohydramnious and symmetrical IUGR. He was born with good APGAR score and severe symmetrical IUGR with low birth weight 1120g (-3.57SDS), length: 36cm (-4.64SDS) and Head Circumference : 26cm (-2.57SDS. He had dysmorphic features; cowlick thick hair, small face, up-slating Palpebral fissure, infraorbital crease, hypertelorism, thin upper lip and dimple chin. Hands and feet: clinodactyly; little finger two phalanges only, single palmar crease and partial overriding toes on the left foot.

He was followed from early in life with multiple specialties for failure to thrive, visual impairment and chronic constipation. Diagnosed with global developmental delay. Recently diagnosed to have ADHD. IQ assessment at age of 5.5 years was 86.

Despite extensive investigation for the chronic constipation that started from early infancy, no cause was found. Subsequently it improved spontaneously. Teeth first erupted at the age of 2 years.

The routine screening for retinopathy of prematurity (ROP) was negative. However, abnormal vascularization was noted at zone III in both fundi. On follow up, he was found to have small eyes with High hypermetropia and Flat cornea. Later fundus examination revealed distinct pigmentary anomalies and retina remained not completely vascularized with presence of retinal vessels in zone III. He was referred to endocrine clinic for short stature at the age of 2 years where he was found to have high IGF1 and normal stimulated growth hormone peak of 31.09 mIU/L.

His short stature believed to be related to a syndromic cause at that stage. His other investigations showed normal brain auditory evoked potential and negative CGH array.

At age of 6 years, whole exome sequencing identified a novel homozygous mutation in IGF1R; NM_000875.4:c.431A>G (p.(Glu144Gly); which correlates very well with his phenotype.

Fig. 1. A. the patient in the first years of life B,C,D. at 10 years of life. note clinodactyl of little finger bilateral

Segregation analysis done for both parents and healthy sibling showed all three are heterozygous of the same mutation.

After getting the molecular genetic result the patient is diagnosed to have a growth hormone insensitivity syndrome and started on growth hormone with a starting dose of (0.047mg/kg/dose six days in a week). His linear growth improved from -3 SD to – 2.3 SD 3 years after treatment.

DISCUSSION

Insulin like growth factors are major regulator of pre and post-natal somatic growth and cellular proliferation. IGF 1 act through a type I IGF receptor. It is also proven, that IGF1 promotes brain, inner ear and retinal development (1–5).

In this case report, we presented a 9.5 years old boy with pre and post-natal growth retardation, dysmorphic features, clinodactyly , visual impairment and delay of mental and psychomotor development. The whole exome sequencing of this patient identified a novel homozygous mutation in IGF1R which correlate very well with the phenotype described.

Up to date only two patients are reported to have homozygous mutation in IGF1R.(6,7)

Our patient in addition to what is described above have prominent visual impairment related to distinct pigmentary anomalies and retina remained not completely vascularized with presence of retinal vessels in zone III. He had moderate response to growth hormone therapy with delta SDs 3 years after treatment was 0.7 which is going with the previously reported response to GH in patient with IGF1R mutations (8).

Test	2.5 years of age	7 years at start of GH	3 years on GH
IGF-1 nmol/L	27.3 (3.5-14.9)	56 (92-34)	94 (11-45)
ng/ml	209 (27-114)	424 (17-269	724 (86-343)
IGFBP3 ng/ml (1660- 2590)	2440		
Max. Stim. GH mIU/L	31.09		

Table 1. hormonal parameters

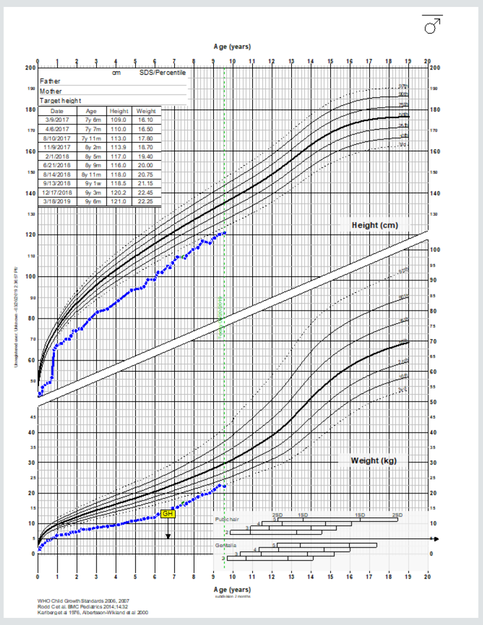

Fig. 2. the growth chart of the patient

CONCLUSIONS

The reported case represent the complicated role that IGF1 play in the human linear growth, brain and eye development. It also showed that these children when identified early they respond to recombinant growth hormone therapy.

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