Severe short stature, Growth Hormone (GH) Deficiency, Hypospadias, and Microcephaly: New Insights into the Role of Chromosome 4 Long Arm Duplication

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INTRODUCTION

Duplication of the long arm of chromosome 4 has been described in more than 60 patients.[1] The severity and specificity of associated symptoms depend on the size and location of the duplication, and which genes are involved. Reported features include developmental delay, intellectual disability, birth defects, hypotelorism, growth retardation, microcephaly, abnormal ears, pointed chin, broad chest, short neck, thin upper lips.[2] Larger proximal duplications may be associated with heart or kidney problems. Most cases are inherited from an unaffected parent with a chromosomal rearrangement called a balanced translocation.

CASE REPORT

We describe a case of a two-year old boy, born at 36 weeks of gestation. The patient was found to have the following: poor weigh gain, short stature (-3 SDS) microcephaly, hypospadias, and horseshoe shaped kidneys. Biochemical evaluation revealed low level of growth hormone after stimulation test 1.45 mcg/L (reference >8 mcg/l) and normal cortisol and thyroid hormone levels. His head circumference was 43.9cm (<3rd percentile) with normal CT head. Developmentally, he met the milestones of gross and fine motor activities and normal eye contact, with delayed speech. Urinary tract ultrasound showed horseshoe shaped kidneys.

Fig.1 Picture of the patient whose details are given above.

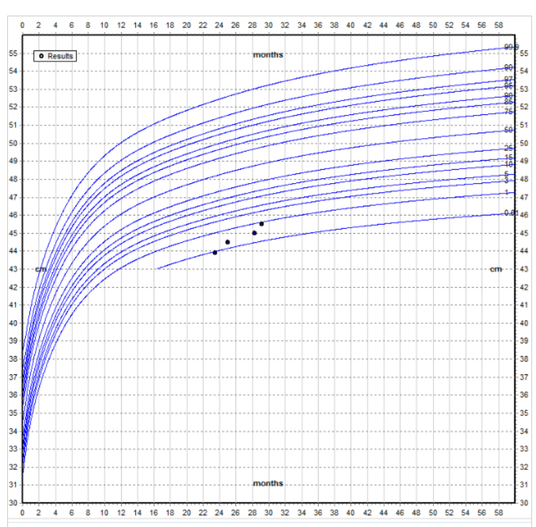

Fig. 2 WHO Head circumference for boys aged 0-5yrs. Head circumference for this patient is indicating a value below 3rd centile

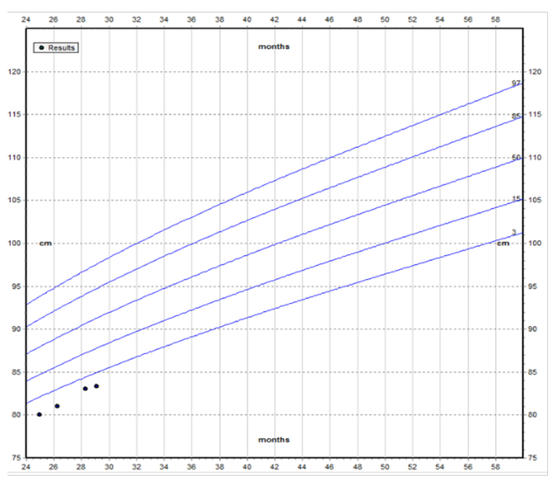

Fig 3. WHO Height for Age 2-5yrs boy showing height below 0.4th centile

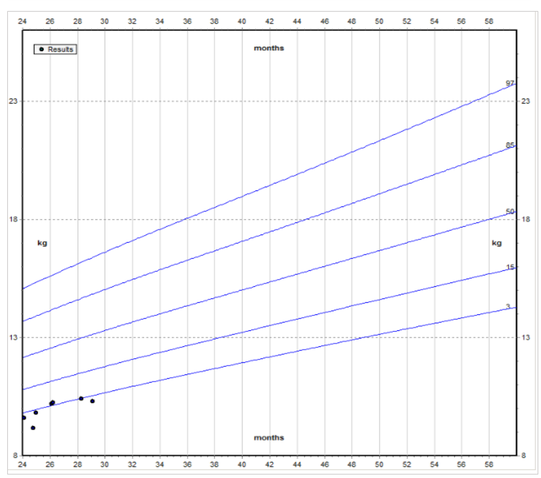

Fig 4. WHO Weight for Age 2-5yrs Boy showing weight below 3rd centile

METHODS

Genome wide oligonucleotide array-based comparative genomic hybridization (aCGH) analysis was performed with use of human genome CGH Microarray kit 44B(OGT technologies).

Chromosomal analysis was done to confirm abnormal aCGH findings.

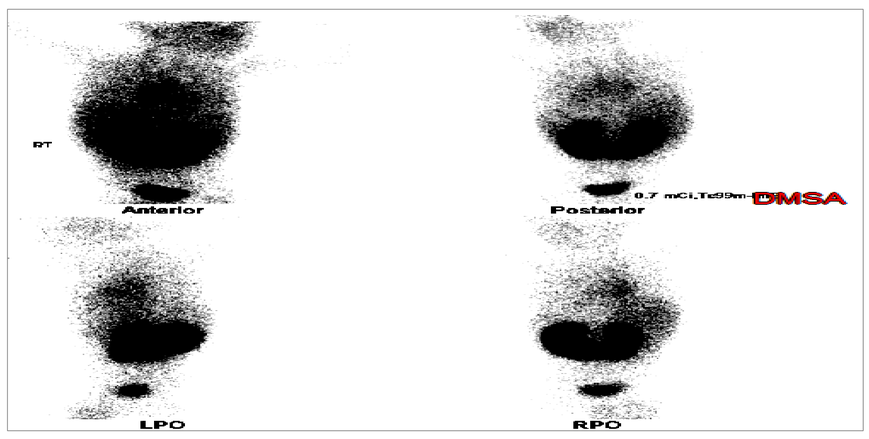

Fig.4 Renal DMSA- Horseshoe kidney noted

Table 1- Biochemical Investigations.

Investigation	Value	Reference range
Growth hormone Provocation test	Maximum Response 1.45mcg/L	> 8mcg/L
IGF	104mcg/L	27.4-113.5mcg/L
IGF binding protein 3	3.24 mcg/mL	0.8-3.9 mcg/mL

RESULTS

- aCGH analysis-gain of approximately 38 MB in the long arm of chromosome 4 extending from cytogenetic band q28 and q32.
- G banding chromosome analysis of 11 metaphase cells from a peripheral blood sample revealed a duplication in the long arm of chromosome 4 at band q28.1 and q32.3.
- Several genes, MMAA (coding for methylmalonic aciduria), FGF2 (coding for fibroblast growth factor 2), NUDT6 (FGF2antisense gene), NR3C2 (involved in mineralocorticoid regulation), and SFRP2 (Wnt signaling pathway) are within the duplicated region observed in the patient.
- FGF2 is involved in limb development, angiogenesis, migration, and differentiation of neuronal cells. Overexpression of FGF2 isoforms in mice results in phenotypic changes, including dwarfism, rickets, hypophosphatemia.[3]

CONCLUSION

- Our patient carries a duplication of chromosome 4 with a cytogenetic band q28 and q32.
- The patient exhibited features related to growth hormone deficiency, short stature hypospadias, horseshoe kidney, and microcephaly.
- The duplicated region has at least 84 known genes taking part in important cellular functions and embryonic development.
- Considering the size and number of genes involved, this imbalance is believed to be causally related to the phenotype seen.
- Our patient expands the spectrum of phenotypes associated with chromosome-4 long arm duplication and further work is on-going to understand the phenotypic features in this patient

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