Short stature in a rare 15q duplication – is hGH treatment beneficial?

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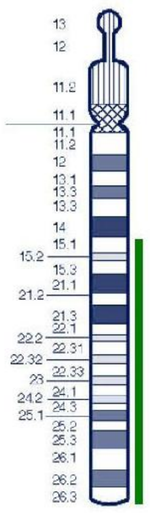
Introduction

❖ Chromosome 15 is frequently involved in the formation of structural rearrangements.
- many of these are associated with an abnormal phenotypes.
- the range and severity of symptoms and physical findings vary from case to case, depending upon the length and location of the duplicated portion of chromosome 15q.
- however, there are consistent and recognizable clinical phenotypes.

❖ Duplication of the long arm of chromosome 15, represents a rare and heterogenous group of chromosomal aberrations.
- first described by Fujimoto et al.in 1974.

❖ Symptoms and physical findings involve:

➢ ***Growth***: - prenatal growth deficiency
- postnatal growth delay.



❖ ***Performance***: - mental deficiency
- learning disability.

❖ ***Craniofacies***: - microcephaly, sloping forehead
- downward slanting palpebral fissures, micrognatia
- proeminent nose with broad nasal bridge,
- midline crease in the lower lip
- long, well defined philtrum, high arched palate.

❖ ***Skeletal***: - scoliosis
- short neck.

❖ ***Hands***: - arachnodactyly
- camptodactily.

❖ ***Others***: - cardiovascular defects, seisures
- minor anomalies in the genital area.

Case Report

✸ **Patient:**
- ➢ 3 years and 7 month old girl
- ➢ was send to Endocrinology Department for ***short stature***

✸ **Family history:**
- ➢ parents – apparently healthy nonconsanguineous
  - mother: 31 y old, height 160 cm
  - father: 31 y old, height 174 cm.
- ➢ brother: 4 y and 10 mo old, apparently healthy
- ➢ parental uncle: 30 y old, height ~ 120 cm.
- ➢ ***parental aunt***: 38 y and 5 mo old
  - diagnosed in infancy with ***pituitary dwarfism*** and ***Turner syndrome*** (mosaicism)
  - height 109.5cm (-9.5SD),weight 23kg (-5.4SD)
  - delayed puberty (secondary sexual characteristics developed ~ 20 y old and menarche at 25 y old with irregular menses)
  - normal morphogram, infanto senescent features : wrinkled skin, small facial skull bones ("doll" face), butterfly wings pigmentation, high voice, acromicria – fig 5,6.
  - somatotropic axis investigations: IGF1<25 ng/ml, small pituitary gland on MRI; adult hGH replacement was proposed.

✸ **Growth development:**
- ➢ *prenatal*: uterine growth delay with arterial pathology at 13 weeks of gestation
- ➢ *birth*: emergency caesarean section at 33 weeks (severe oligohydramnios) : weight : 1200g (S.G.A., -2.8 SD), height: 38cm, -3.4SD, Apgar 7 at 1 minute.
- ➢ *postnatal*: developmental delay
  - didn't speak until 2 years of age
  - walked at 2 years and 1 month
  - limited understanding (partialy due to transmission deafness later diagnosed).

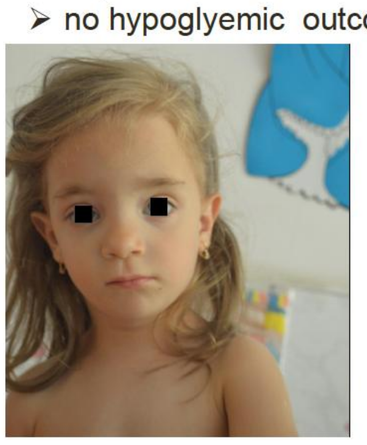
✸ **Symptoms:**
- ➢ hypoglycemic episodes (40-63 mg/dl)

✸ **Clinical examination at 2 y and 5 mo:**
- ➢ height at – 5.38 SD: 74 cm, weight 7000g
- ➢ delayed bone age (1 y and 6 mo)
  - growth prognosis at 160.5 cm
- ➢ particular features - fig .1, 2
  - big forehead, small triangular facies, micrognathia
  - proeminent nose, broad nasal bridge , anterior fontanelle open
  - long philtrum, low set years
- ▪ *first diagnosed with Silver Russell syndrome*
- ▪ ruled out by - molecular investigations

- FISH analisys: de novo" interstitial chromosome 15 duplication **15 (q21.2 to q24.1)**

✸ **Investigations:**
- ➢ celiac desease markers - negative.
- ➢ thyroid function was normal
- ➢ MRI - small pituitary gland.
- ➢ hGH replacement was initiated : 0.043 mg/kg per day

✸ **After 1 year and 4 months of treatment:**
- ➢ height improved at - 4.97 DS (83 cm), growth rate 0.56 cm/month- fig.4
- ➢ weight 9000g, bone age ~ 2years - fig. 3
- ➢ improved IGF1 at 81.07 ng/ml (N: 13-187)
- ➢ no hypoglyemic outcomes.



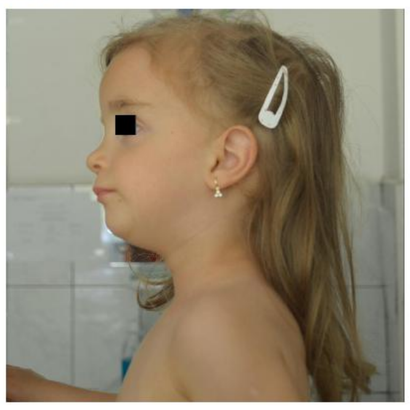


Fig. 1 and fig . 2 - particular features

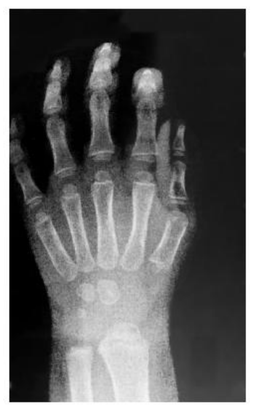


Fig. 3 – Bone age delay

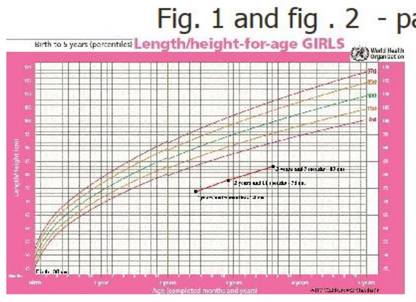
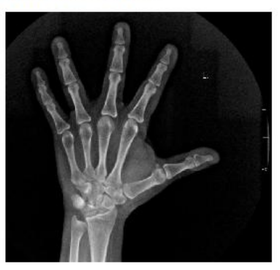


Fig. 4 – Growth rate with treatment



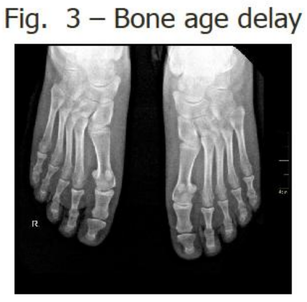


Fig. 5 and fig. 6 - Acromicria

Discussions

❖ Even though chromosome 15 is very much involved in the formation of structural rearrangements, the duplication of the long arm represents a rare heterogenous group of chromosomal aberrations.

❖ Mutations on this region are inducing extremely different phenotypes, depending on the precise location and the lenght of the mutation.

❖ Breakpoints vary and while some individuals have an interstitial duplication (with two breakpoints), others have a duplication of the end of the chromosome.

❖ We present an unique case of distal 15q duplication with the breakpoint that lies between 15 q21.2 and q24.1.

❖Short stature is common in this particular chromosomial disorder.

❖ In our case, treatment with high doses of hGH ameliorated growth velocity and prevented other hypoglycemic episodes.

❖ On a long term, hGH replacement could be beneficial and improve the quality of life and a better social integration for this rare individuals.

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