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, micrognathia
  - prominent nose with broad nasal bridge.
  - midline crease in the lower lip
  - long, well defined philtrum, high arched palate.

Skeletal: scoliosis
- short neck.

Hands: arachnodactyly
- camptodactyly.

Others: cardiovascular defects, seivures
- 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 nonconsangineous
    - 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 dwarfish and Turner syndrome (mosiacism)
      - 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, infantile senescent features wrinkled skin, small facial skull bones (“doll” face), butterfly wings pigmentation, high voice, acromia – fig 5.6.
      - somatotopic 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 oligohidramnios)
    - 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 (partially due to transmission deafness later diagnosed).

- Symptoms:
  - hypoglycemic episodes (40-63 mg/dl)
  - Clinical examination at 2 y and 5 mo:
    - height at ~ 83.8 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
  - prominent nose, broad nasal bridge, anterior fontanelle open
  - long philtrum, low set years
  - first diagnosed with Silver Russell syndrome
  - ruled out by - molecular investigations
  - FISH analysys: de novo interstitial chromosome 15 duplication 15q21.2 to q24.1

- Investigations:
  - celiac disease 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 hypoglycemic outcomes.

- Fig. 1 and fig. 2 – particular features
- Fig. 3 – Bone age delay
- Fig. 4 – Growth rate with treatment
- Fig. 5 and fig. 6 – Acromia

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 length 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 15q21.2 and q24.1.
- Short stature is common in this particular chromosomal 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.

References:
2. Rare Chromosome Disorder Support Group, Oxford, Surrey. 15q duplications. Web June 2009