Differential diagnosis of pre- and postnatal short stature revisited: 3-M Syndrome

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INTRODUCTION

- synonyms: 3-M Syndrome, Three-M Slender Boned Nanism,
  Yakut Short Stature Syndrome
- rare autosomal recessive disorder,
- first described by Miller, McKusick and Malvaux
- frequency < 1/1,000,000,
  - Prevalence 200 reported cases

CRITERIA

- Signs:
  - –Pre- and postnatal disproportionate short stature, Micromelia, relative Macrocephaly
  - –radiological bone dysmorphism
- Identification at birth:
  - ➢Low birth weight
  - ➢characteristic „gloomy" face: relatively large head, dolichocephaly, balcony forehead, triangular face with pointed chin, upturned nostrils, full lips, dense eyebrows, long philitrum and a midface hypoplasia.
  - ➢short neck, prominent trapezius muscles, square shoulders, a short thorax with a funnel or chicken breast, hyperlordosis, abnormally increased mobility of the joints and shortened little fingers.
- To confirm the diagnosis: Mutation (recessive) in one of the three genes:
  - 3M syndrome 1 (67-75%): CUL7 gene, chromosome 6; cullin 7 protein
  - 3M syndrome 2 (20-28%): OBSL1 gene, chromosome 2; Obscurin-like protein 1
  - 3M syndrome 3 (5%): CCDC8 gene, chromosome 19; Coiled-coil domain-containing protein 8

RESULTS

Findings:

Physical examination:

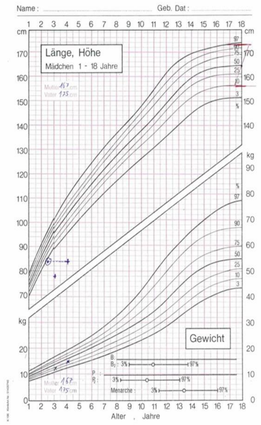
- Body height: at 10 mo. 61.5 cm (<-5 SDS), at 3 1/12 yr. 77.8 cm (<-4 SDS),
  at 4 4/12 yr. 83.6 cm (<-4 SDS)
- Disproportional growth, torso height of 48.2 cm, based on a total height of 83.6 cm (> +10 SDS),
- Ratio of subischial leg height to trunk height: 0.76 (<-6 SDS) markedly decreased

Radiological findings:

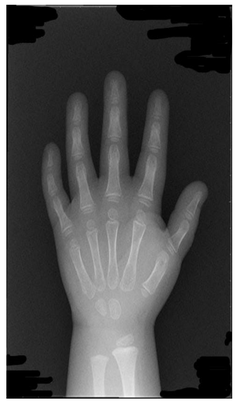
- missing 12th ribs
- Signs of *spondyloepiphyseal dysplasia*
- Bone Age 2 6/12 Jr., Chronological 4 1/12 Jr.

Growth factors: IGF-I 99 ug / L (SDS -0.14), IGF-BP3 3.48 mg / L (SDS 1.81)

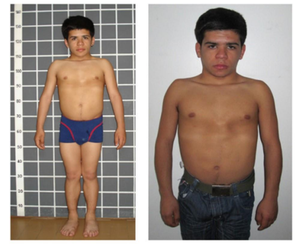
Genetics: *Mutation in the CUL7 gene*: CUL7: c3041 [T> G]; [T> G].



+ Chronol. Age
. Bone age



Bone Age 2 6/12 Jr.



(a) 15 years (b) 17.5 years

Image of a young boy with Three M Syndrome at 15 (a) and 17.5 (b) years old showing facial dismorphism, short stature, broad thorax, sternum carinatum.
Source: https://www.dovemed.com/diseases-conditions/three-m-syndrome/ ‚Three M Syndrome' Update Sept. 3, 2019

Treatment:

- Improvement of short stature through surgical bone lengthening or growth hormone substitution therapy.
- skeletal abnormalities: orthopedic techniques and surgery
- cranio-facial anomalies: plastic surgery
- dental abnormalities: corrective procedures
- eventually physiotherapy

Monitoring:

- hip ultrasound scan to screen for developmental dysplasia
- endocrinological monitoring of the growth and pubertal progress.

Differential diagnosis of pre- und postnatal short stature:

- ➢ 3M syndrome
- ➢ Silver-Russel syndrome
- ➢ Bloom syndrome
- ➢ Dubowitz syndrome
- ➢ Rubinstein-Taybi syndrome
- ➢ Floating Harbor syndrome
- ➢ Mulibrey nanism
- ➢ fetal alcohol syndrome

CASE REPORT

Case:
4 4/12 Jr. old girl:

- Short stature
- Body disproportion

Birth history:

- Secondary cesarean section in the case of birth arrest after 41 + 5 weeks of gestation
- Weight at birth: 2430 g (<3.P, [-2.2 SDS])
- Body length 44 cm (<3.P, [-3.5 SDS])
- Head circumference 33.5 cm (10th-25th P)

Prenatal diagnosis: thickened neck fold (3.7cm)
➔Chorionic villus sampling: normal
Postnatal: U2 shortened long bones,
especially of the upper extremities

CONCLUSIONS

Differential diagnosis of pre- and postnatal short stature.

Children with 3M syndrome develop disproportionate short stature with conspicuous radiological signs. The diagnosis is confirmed by detection of mutations in one of the three genes:CUL7, OBSL1 or CCDC8

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