Clinical Genetics: Case Studies

Read the following case studies and answer the questions.

Case 1: 10q26del Syndrome in a female infant

- **Prenatal hypotrophy + psychomotor retardation + dysmorphism**
- Pregnancy and perinatal period:
    - Normal karyotype obtained from amniotic fluid (*why was this performed?)*
- Pelvic presentation
- 37 weeks of gestation.
- Weight: 2230g (*please mark on the growth chart on page 3*)
- Length: 48cm (*please mark on the growth chart on page 4*)
- Head circumference: 33 cm (*please mark on the growth chart on page 5*)

Medical History:

She didn't want to suckle while breastfeeding (*is that significant?*) She is currently bottle-fed suitable to her age.

Two hospitalizations: due to rota- and flu-like diseases

Iron-deficiency anemia postpartum, now constipation (after Fe treatment?)

Physical Exam / Labs:

Physical parameters 6mo. age: 5.6kg (*determine percentile*), length: 61cm (*determine percentile*), head circumference 39 cm (*determine percentile*)

She turns from abdomen to back, raises her head, is unable to sit unsupported

Inactive, no hypotonia

Dysmorphism of the craniofacial area (closed anterior fontanelle, preauricular tag, ... *please describe other features, see images on page 2*), bilateral transverse palmar crease, without major malformations.

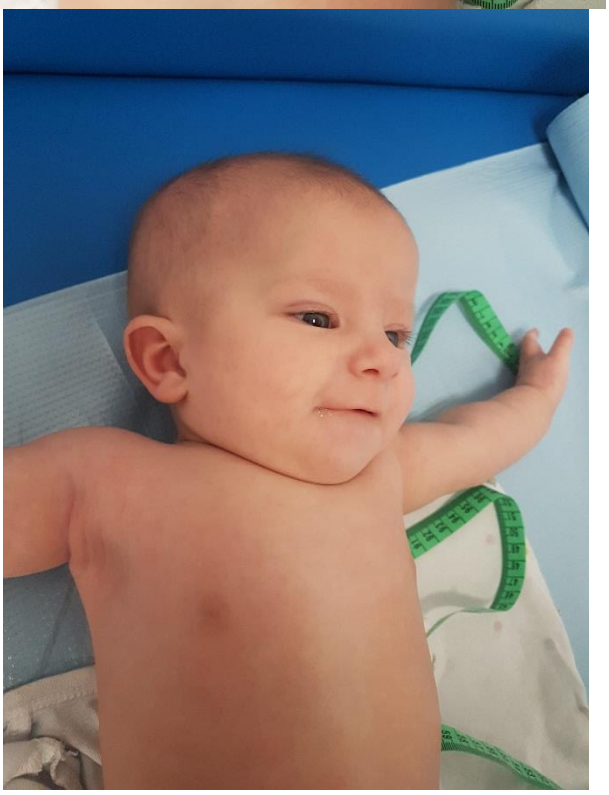
Genetic test results: Whole-genome oligonucleotide microarray

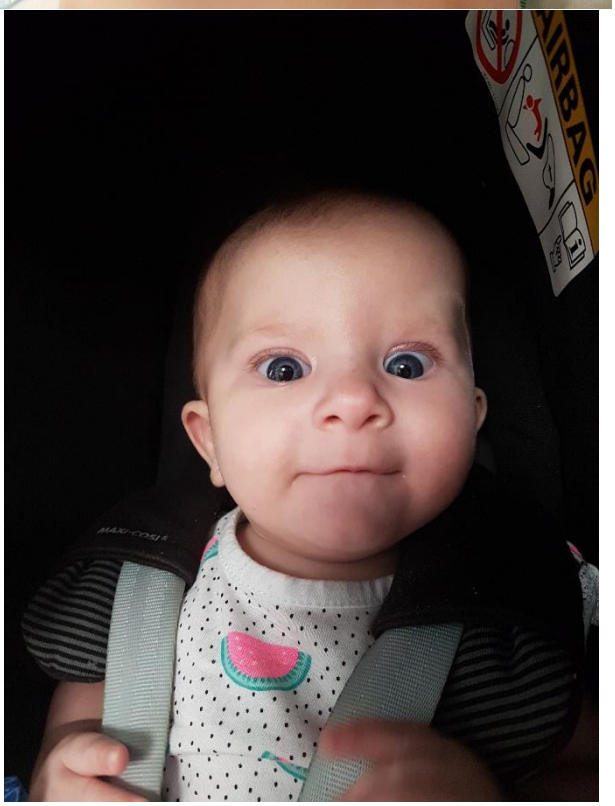
Results are abnormal. A deletion in the genome was found in the long arm of chromosome 10 in the 10q26 region of 10.06 Mbp size. The deletion contains many genes and is considered pathogenic . A consultation with a clinical geneticist is warranted. Cytogenetic testing is necessary in order to assess the paternal origin of the confirmed deletion as well as for genetic counselling.

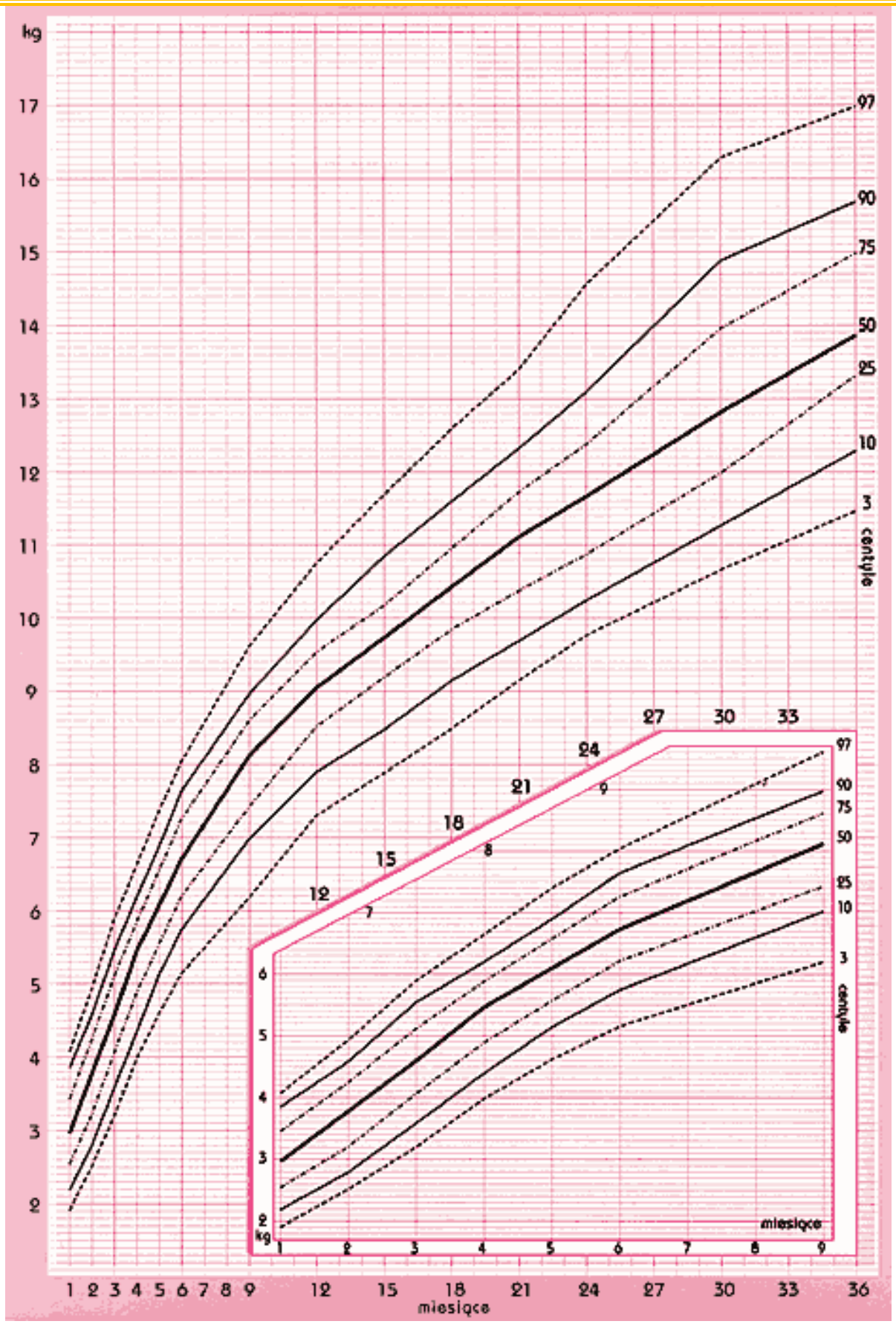
For more information about this deletion, please visit:

https://omim.org/entry/609625 (choose clinical synopsis in that page)

Which of this syndrome's symptoms best matches the clinical picture?



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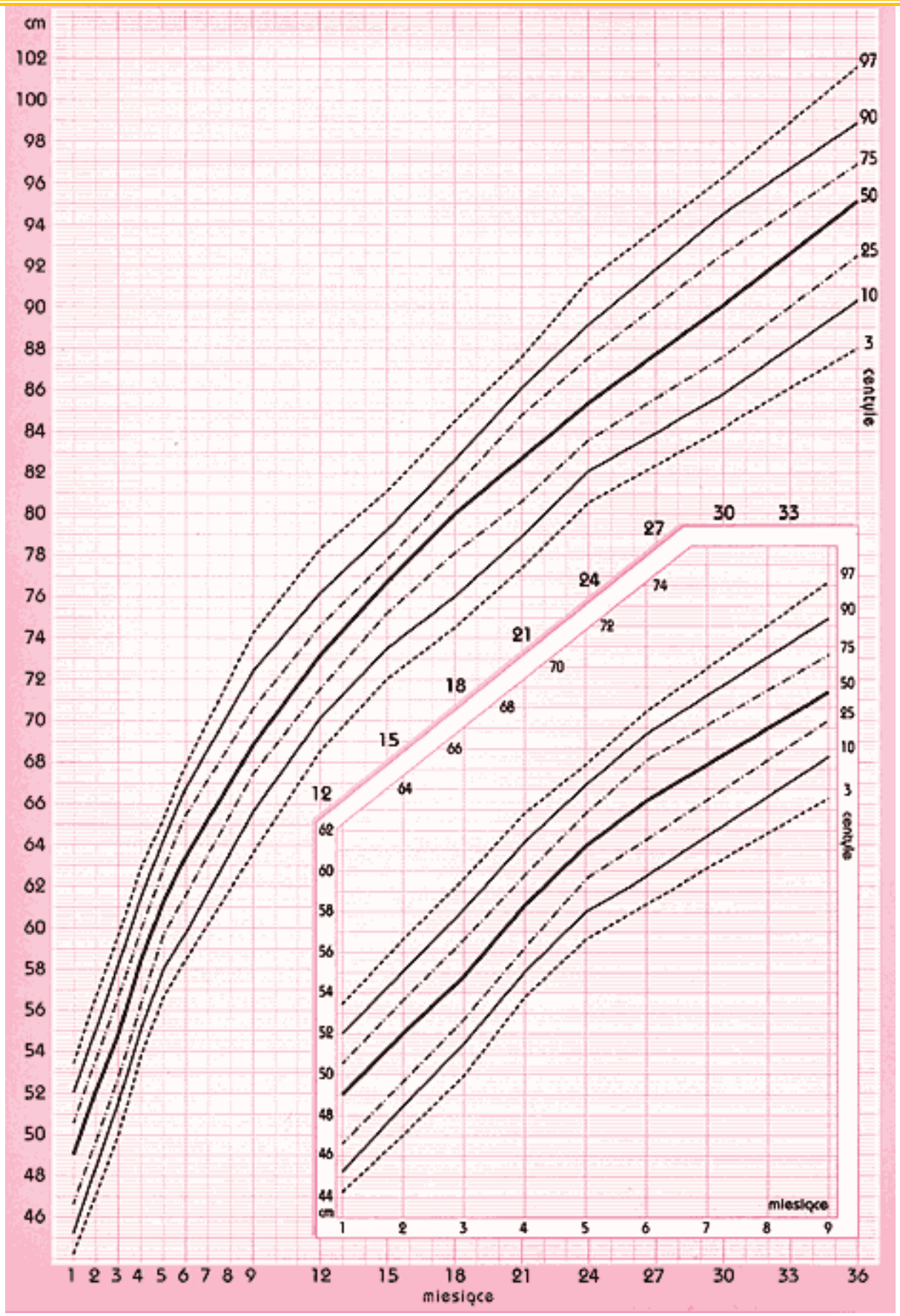
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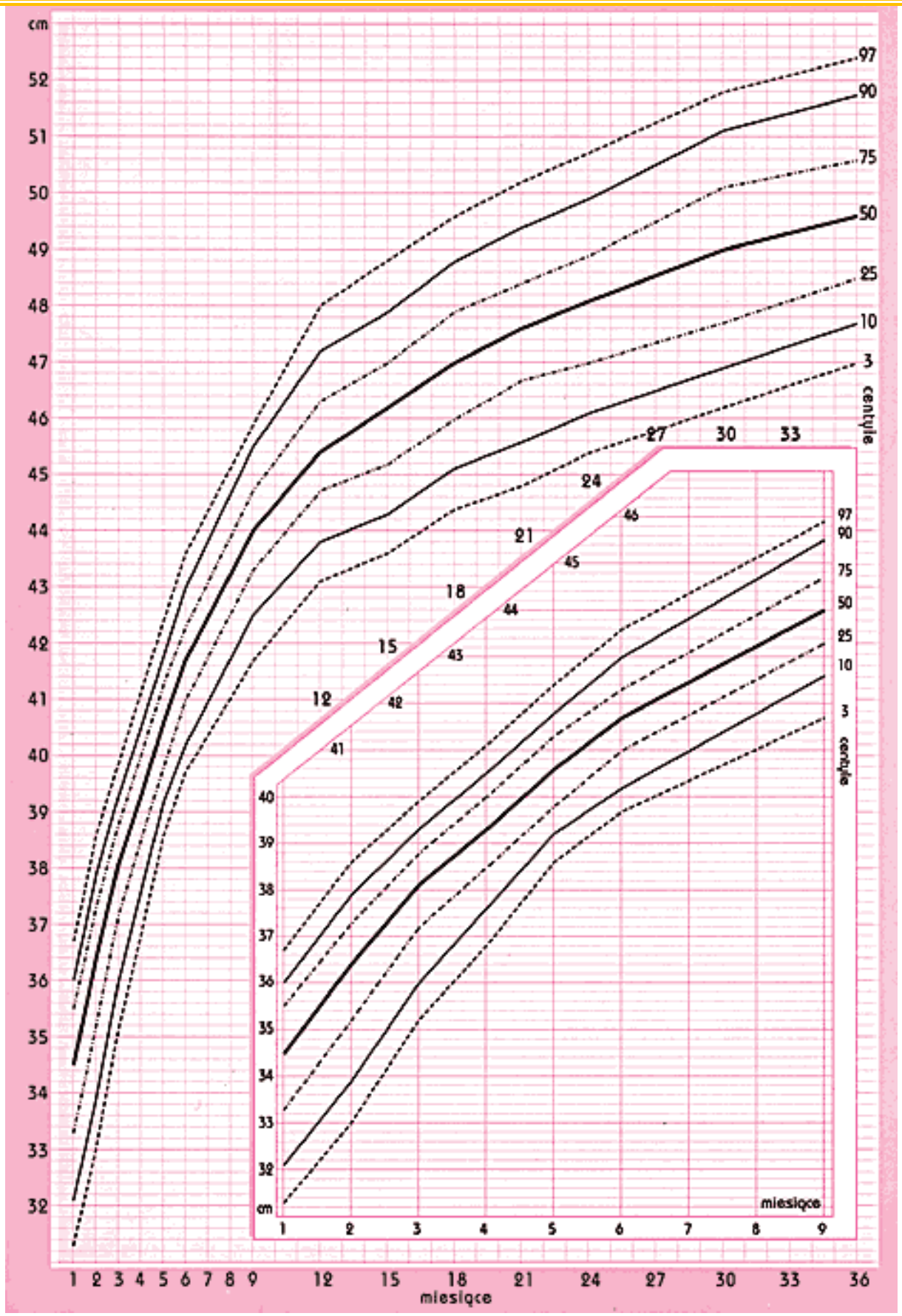
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Case 2:

18-year-old man referred by an endocrinologist:

- learning difficulties at a vocational school

- obesity with atypical fat distribution

- prominent ears

- genu valgum

- testicles: small and hard on touch

Family history without similar problems.

PROPOSALS *(Tasks for you)*

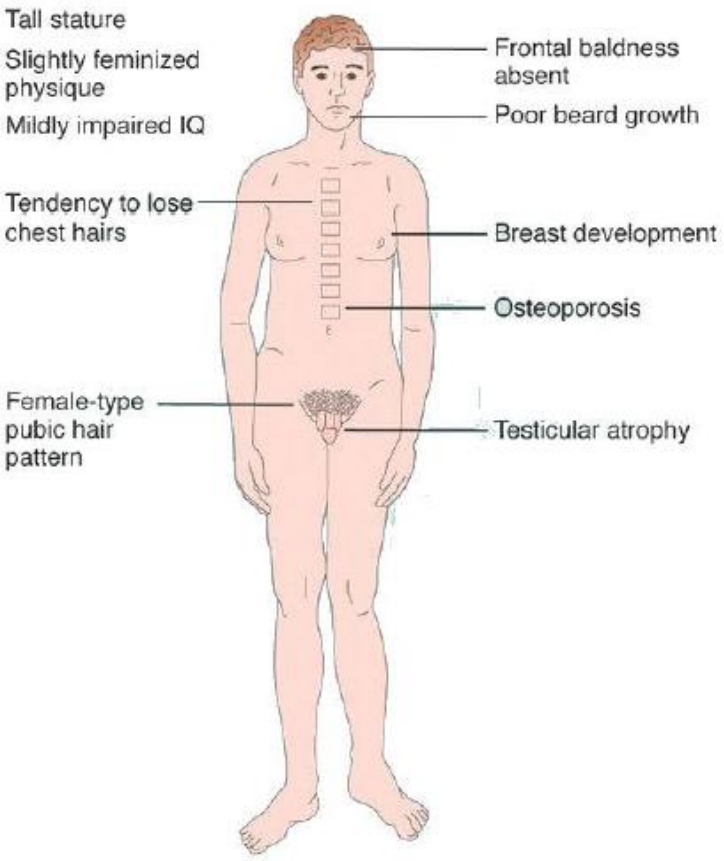
1. What genetic tests will you propose?

2. Suggest a diagnosis.

3. Based on the above information, outline a treatment plan.

4. How would you identify this syndrome prenatally?

5. The fate of the pregnancy - current laws pertaining to termination of pregnancy in your country.



KARYOTYPE TEST RESULTS: 47, XXY:

Abnormal male karyotype with an additional X chromosome in all cells analyzed. This confirms the diagnosis of Klinefelter syndrome.

INTERPRETATION: The karyotype test results are sufficient for the diagnosis of Klinefelter syndrome in this patient.

It is a genetic disease, caused by sex chromosome trisomy detected in a cytogenetic test. The key symptoms are hypogonadism, hypogenitalism, abnormal puberty associated with insufficient testosterone production and fertility disorders resulting from abnormal testicular function. Learning difficulties or ADD may be present. The patient’s movement disturbances as well as dysmorphism are consistent with the diagnosis of Klinefelter's syndrome.

Consultation with an endocrinologist is recommended in order to consider indications for hormone substitution therapy.

RECOMMENDATIONS:

1. Further endocrinological care (possible testosterone supplementation as in Klinefelter syndrome), psychological, neurological and pediatric care.

2. In case of questions or doubts, please contact us by phone: 1234565.

Case 3: Coffin-Siris Syndrome

Medical History:

Significant retardation of physical development + psychomotor delay + numerous dysmorphic features

Pregnancy and perinatal period:

39 weeks of gestation; 2190g; 47cm; head circumference 34cm.

Physical parameters at 3 years and 6mo. of age:

10.5kg (<3rd pc); 85cm (<< 3pc); head circumference 42cm (<< 3pc)

Developmental defects / dysmorphism:

Congenital microcephaly; submucous cleft palate; spina bifida; nystagmus; laryngeal rotation; nephrocalcinosis; hip dysplasia;

Other medical problems:

Mixed hearing loss; pylorostenosis; immunodeficiency; atopic dermatitis.

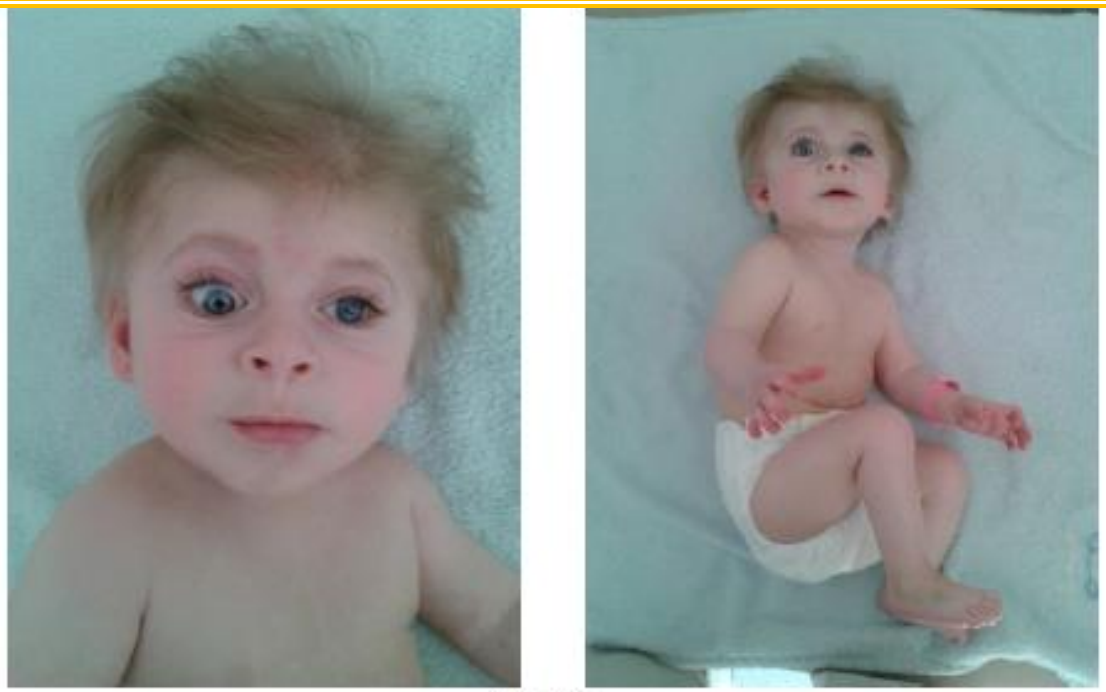
Additional test results:

- MRI of the head at age 22mo. showed bilateral cysts and thinning of nn. II, corpus callosum hypoplasia

- fundus examination: bilateral fissure of optic disc

TASKS:

1. Describe the dysmorphism pathognomonic to this syndrome.
2. Suggest diagnostic tests.
3. State the risk of cancer in this syndrome.
4. NGS panel dedicated to SWI / SNF spectrum diseases: a new pathogenic missense variant in *SMARCB1* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499322/).



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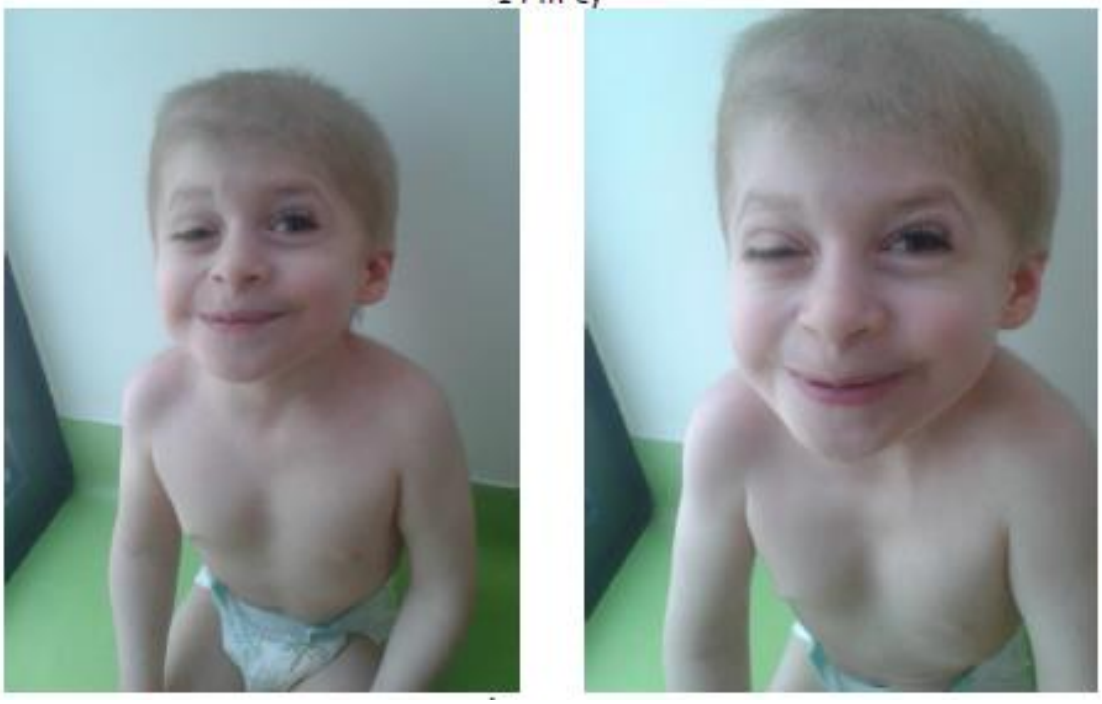

Patient at 3yrs and 5mo. of age

Case 4: Cerebellar Ataxia

2.5yr child with cerebellar ataxia – suspicion of ataxia-telangiectasia.

Film presenting four examples of ataxia (cerebellar dysfunction).

https://www.youtube.com/watch?v=-s77voH8nRI

Tasks:

1. Describe the clinical problems you see in the videos.
   Note Video 3: Ataxia-telangiectasia (+ conjunctival telangiectasia)
2. List the diagnostic tests you would perform.
3. List your recommendations for the other, healthy family members.

Case 5: 7yr old boy:

- Speech delay (only says simple phrases)
- Hypotonia during the first year of life + suckling disturbance
- Recurrent AOM + hearing impairment
  (2x ear drainage: without hearing impairment)
- Discoloration marks on the left lower abdominal area.
- Body mass 30kg; height 134cm

Tasks:

1. Describe the dysmorphism
2. Differential diagnosis?
   https://www.omim.org/ (search "ptosis and hypertelorism and chest")
3. Final diagnosis?
4. Propose a treatment plan.

Notes on the *Cell-free Fetal DNA NIFTY test (cffDNA): Read before Cases 7-11.*

- DNA circulates freely in maternal blood. So…
- Simply take a blood sample from the mother.
- Analysis of cffDNA is non-invasive, prenatal diagnosis.
- Target patient: pregnant women of advanced maternal age.
- cffDNA is no longer detectable in maternal blood 2 hours after delivery.
- It is a rather sensitive test. It assesses the *risk* of chromosomal aberrations quite well. However, its results should be confirmed by an *invasive* test (amniocentesis).
- We need at least 3-4% fetal fraction in order to reach any conclusion. If there's any less than that, the result is inconclusive.[k1]

Case 7: Noninvasive genetic test NIFTY: cffDNA analysis

Gestational age: Week 14, Day 1

Test results: Abnormal results – high risk of Trisomy 21.

- Risk of Trisomy 21: 1 / 1.01
- Risk of Trisomy 18: 1 / $1.7x10^8$
- Risk of Trisomy 13: 1 / $1.1x10^9$

Number of sex chromosomes: no abnormalities found.

Fetal sex: M. cffDNA: 8.5%

Patient history: 3rd pregnancy; 2nd childbirth. USG during the 12th wk: nuchal translucency 2.1mm + PAPPA test 1/15 risk of trisomy 21.

Interpretation of results: a high risk of Trisomy 21 was found, which corresponds to the likelihood of the fetus being affected by Down's Syndrome. The risk of other disease presence is low. Consultation with a clinical geneticist is warranted. Invasive diagnostics (amniocentesis) is recommended in order to verify the identified risk, because the NIFTY result may be falsely positive due to limited placental mosaicism.

Case 8:

Gestational age: Week 14, Day 1

Test results: Trisomy 21, High risk (>99%).

Further recommendations: consultation with a clinical geneticist and further diagnostics are warranted.

Case 9:

Gestational age: Week 13, Day 0. Number of fetuses: 1

Results: Microdeletion in region 22q11.2

Comment: The above results pertain to a screening test. Thus, results may be false positive or false negative.

Patient history: First pregnancy after IVF. USG during the 13th week: nuchal translucency 1.3mm.

Case 10:

PATIENT INFORMATION		REFERRAL INFORMATION	
NAME **tt6 normal**		CLINIC NAME **XXXXXXXXX**	
ID NUMBER **893247**		CLINIC ID **331**	
DATE OF BIRTH (DD/MM/YYYY) **02/03/1985**	GESTATIONAL AGE **Week: 12 Day: 0**	REFERRING CLINICIAN **Dr.XXXXXXXXXXX**	
IVF STATUS **No**	NUMBER OF FETUSES **One**	CLINIC FAX **000000000000000000**	
SAMPLE INFORMATION			
ORDER NUMBER **V302787**	LAB NUMBER **567567**	DATE OF COLLECTION (DD/MM/YYYY) **20/08/2017**	DATE RECEIVED (DD/MM/YYYY) **20/08/2017**

VERACITY PRENATAL SCREENING TEST RESULTS

NEGATIVE for aneuploidies and microdeletions

FETAL FRACTION

5.7%

CONDITION	REMARK
Trisomy 21	The results show very low risk for trisomy 21
Trisomy 18	The results show very low risk for trisomy 18
Trisomy 13	The results show very low risk for trisomy 13
Trisomy X	The results show very low risk for trisomy X
Monosomy X	The results show very low risk for monosomy X
XXY Constitution	The results show very low risk for XXY constitution
XYY Constitution	The results show very low risk for XYY constitution
Microdeletions: (DiGeorge,1p36 deletion syndrome,Smith-Magenis, Wolf Hirschhorn)	The results show very low risk for microdeletions (DiGeorge (22q11), 1p36 deletion syndrome, Smith-Magenis (17p11.2), Wolf Hirschhorn (4p16.3))
Presence of Y Chromosome	The results show the presence of Y chromosome

INTERPRETATION

The results show very low risk for all tested conditions. The fetal fraction is 5.7%, which is sufficient for analysis.The results should be communicated by the referring clinician with appropriate counselling.

Case 11:

PATIENT INFORMATION		REFERRAL INFORMATION	
NAME **Sample 1**		CLINIC NAME **New Testing Clinic**	
ID NUMBER **389274**		CLINIC ID **446**	
DATE OF BIRTH (DD/MM/YYYY) **25/03/1985**	GESTATIONAL AGE **Week: 13 Day: 0**	REFERRING CLINICIAN **Dr. New Doctor**	
IVF STATUS **No**	NUMBER OF FETUSES **One**	CLINIC FAX	
SAMPLE INFORMATION			
ORDER NUMBER **V977146**	LAB NUMBER **678**	DATE OF COLLECTION (DD/MM/YYYY) **05/06/2018**	DATE RECEIVED (DD/MM/YYYY) **05/06/2018**

VERAgene PRENATAL SCREENING TEST RESULTS

VERY LOW RISK NIPT Results

FETAL FRACTION

8.9%

CONDITION	REMARK
Trisomy 21	The results show very low risk for trisomy 21
Trisomy 18	The results show very low risk for trisomy 18
Trisomy 13	The results show very low risk for trisomy 13
Trisomy X	The results show very low risk for trisomy X
Monosomy X	The results show very low risk for monosomy X
XXY Constitution	The results show very low risk for XXY constitution
XYY Constitution	The results show very low risk for XYY constitution
XXYY Constitution	The results show very low risk for XXYY constitution
Microdeletions: (DiGeorge,1p36 deletion syndrome,Smith-Magenis, Wolf Hirschhorn)	The results show very low risk for microdeletions (DiGeorge (22q11), 1p36 deletion syndrome, Smith-Magenis (17p11.2), Wolf Hirschhorn (4p16.3))
Panel of 50 single gene diseases	The results show very low risk for the panel of 50 monogenic diseases
Presence/Absence of Y chromosome	The results show the presence of Y chromosome

INTERPRETATION

The results show very low risk for all tested conditions screened. The fetal fraction is 8.9%, which is sufficient for analysis. The results should be communicated by the referring clinician with appropriate counselling.