Trisomy 21

The most frequent viable chromosome disease. Like other inborn autosomal chromosome diseases, associates dysmorphia + psycho-motor delay, and possible visceral malformations (found in more than 1/3 of cases); a medico-pedagogic care and follow up must be undertaken.

I. EPIDEMIOLOGY

(a question on epidemiology would also include recurrence risks according to the karyotypic findings: see paragraph on the karyotype).

1.5 /1 000 births.

Sex ratio: 3 males/2 females.

Increased median maternal age (34 years).
Maximal trisomy 21 births from mothers aged:

- 28 yrs (but this is only because the maximal birth rate is for this maternal age).
- Around 37 yrs.
- The risk increases with maternal age: <0.1% below 30 yrs; between 0.1% and 1% at ages 30-40 (0.2% at 34 yrs, 0.5% at 38 yrs, 0.7% at 39 yrs); >1% above 40 yrs (5% at 46 yrs, 15% at 50 yrs).

II. CLINICAL EXAMINATION

1 - Dysmorphic syndrome associating (to various extend):

- evocative face +++:
  - frequent microcephaly, short neck, flat occiput and brachycephaly;
  - moon-shaped face;
  - flat nasal bridge;
  - "socket" nostrils;
  - hypertelorism (or pseudo-hypertelorism);
  - epicanthus (regresse with age);
  - upward slanting palpebral fissures;
  - Brushfield spots in the iris (pathognomonic, detectable in blue eyes).
- macroglossia; glossitis exfoliativa (geographic tongue); scrotal tongue at late childhood and in adulthood;
- mouth frequently open; frequently open mouth;
- narrow/ high arched palate; high arched narrow palate;
- late appearing/malformed teeth (numerical anomalies, agenesis of lateral incisors...);

- hands and feet:
  - short and broad;
  - brachymesophalangia of the 2nd and 5th fingers;
  - clinodactyly of the 5th finger;
  - flat feet;
  - first toe set apart from the others by a gap, with a crease.

- dry skin, mottled skin (livedo), with frequent infections around orifices.
- hyperlaxity of ligaments.
- frequent umbilical hernia.

2 - Psycho-motor delay (constant):

- hypotonia +++ at birth (hold his head at 6 mths, sits at age 1 yr, walks at age 2 yrs).
- the mental retardation, not obvious in the infant, will soon become manifest.
- children's behaviour:
  - affectionate, gentle, cheerful;
  - language difficulties;
  - like to play, to mime, to tidy up meticulously;
  - normal memory.

- seizures (in 3% to 9%, as compared to 1% in the general population).

3 - Dermatoglyphics:

- transverse palmar crease in 75% of cases. Beware: it is also present in 1% of the general population; therefore, out of 8 transverse palmar creases at birth, 7 come from the general population and only 1 from a Down syndrome baby (1% risk X 699/700 births versus 75% risk X 1/700 births); one MUST NOT make a diagnosis of trisomy 21 on this isolated sign and throw parents into a panic.
• axial triradius in %t (in 75%).
• transversality index > 30.

This association of signs implicates that visceral malformations have to be searched for, as they can burden the vital prognosis and impose that emergency treatments be started.

4 - Malformations (45% of cases):

- Heart (40%):
  - atrioventricular septal defect (10 %);
  - ventricular septal defect (10 %);
  - patent foramen ovale (5 %);
  - persistence of ductus arteriosus (5 %)...

- Digestive (10 %):
  - duodenal stenosis (1/3 of duodenal stenosis are found in trisomy 21 patients);
  - imperforate anus...

- Ocular:
  - cataract (congenital or acquired);
  - astigmatism;
  - myopia;
  - strabismus;
  - congenital glaucoma;
  - nystagmus.

5 - Other:

- Hematologic:
  - transient leukemoid reaction may occur
  - sometimes with a relapse as acute leukemia (lymphoblastic (ALL) or more frequently non-lymphoblastic (ANLL) leukemias; M7-ANLL (megakaryocytic) is particularly frequent. Watch the hypersensitivity to methotrexate.

- Immunological:
  - tuberculin hyporeactivity;
o immune deficiency.

- Metabolic:
  o hyperuricemia;
  o abnormal glycemia;
  o increased TSH (frequent); hypo or hyper thyroidy.

III. DIAGNOSIS: THE KARYOTYPE

proves the diagnosis, allows/implicates a genetic counseling: recurrence risk is about 1 % if the anomaly is de novo, more if one of the parents is a translocation carrier.

**Free and homogeneous trisomy 21** (92,5 % of cases):

- sporadic (de novo) cases.
- role of maternal age (see above in epidemiology).
- recurrence risk: 1 to 2 %.
- karyotype: 47,XY,+21 ou 47,XX,+21.
- due to meiotic non-disjunction:
  o of maternal origin:
    - 1st division: 70 %
    - 2nd division: 20 %
  o of paternal origin:
    - 1st division: 5 %
    - 2nd division: 5 %

**Free trisomy 21 in mosaic** (2,5 % of cases):

- sporadic cases.
- karyotype: 46, XY / 47, XY,+21 or 46, XX / 47, XX,+21.
- post zygotic event (mitotic).
- most often, the phenotype is typical, at times attenuated.

**Trisomy 21 due to translocation:**
• de novo or transmitted from a parental translocation (being a balanced translocation in the parent); genetic counseling is especially needed in the latter case.
• karyotype with 46 chromosomes; the extra chromosome 21 is most often translocated with another acrocentric (groupe D: 14, 13 or 15 or groupe G: 21 or 22) chromosome; example: 46, XY, t(14;21).
• genetic counseling and recurrence risk:
  o t(Dq;21q) et t(21q;22q)
    of maternal origin: risk = 15 %
    of paternal origin: risk = 5%
  o t(21q;21q): risk = 100 %:
    either --> trisomy 21
    or --> spontaneous miscarriage (monosomy 21).
  o Other:
    • partial trisomy 21 (rare). --> (the segment responsible for most of the syndrome/phenotype is band 21q22.3.
    • associated with other chromosome anomalies (rare).

IV. EVOLUTION

• statural delay (adult = 1,50 m); weight excess (--> diet).
• voice becomes hoarse.
• pelade may appear.
• puberty is delayed but normal; poor libido;
• fecondity in the female ( --> contraception).
• hypothyroidy, Basedow (--> T3, T4, TSH, reverse T3 regular determination).
• mental development:
  o intelligence quotient (IQ) = 50 (mean (and median)); between 30 and 80; Gaussian curve, as in the general population but with a mean shift to 50 instead of 100; vary according to age);
  o social insertion: partly according to the familial environment, the guidance and reassurance that the family receives, and according to the medical, paramedical, and pedagogic cares instaured;
  o psychomotor therapy from the age of 6 mths, kinesitherapy, orthophony latter; nursery school, followed if possible by a class of handicapped children within a normal primary school; latter, school and professional
school in specialized institutions; apprenticeship, manual professionnal activity; insertion into active life; they must not stay at parents home, where they would remain with a child status, and finally where they would grow old faster as parents get old.

- early aging:
  - behaviour may suddenly switch from that of a happy and sociable child to a sad, inactive and inexpressive adult;
  - risk of senile dementia (Alzheimer disease).

V. PROGNOSIS

- life expectancy, formerly poor, has greatly increased, due to antibiotherapy and surgery.

- prognosis can be impaired by:
  1 - the extreme susceptibility to infections.
  2 - malformations, cardiac malformations in particular.
  3 - acute leukemia (in 1 % of trisomy 21 infants/children, i.e. 20 times more frequently than in the general population).

- intellectual prognosis: (see evolution).

VI. TREATMENTS

- surgery in the case of malformation(s).
- antibiotherapy of infections; antifungal treatment of athletic foot.
- medical-paramedical-pedagogic cares; psychomotor therapy, kinesitherapy, orthophony.
- thyroid function repeated examinations (once a year).
- ophtalmologic tests (watch the hypersensitivity to atropine), auditive tests.
- cervical X-rays (cervical instability→ risk of cervical vertebrae dislocation).
- flat foot (special shoes, tricycle are recommended).
- flat dorsum (swimming recommended).
- keloid scars (surgery only when needed, avoid plastic surgery).
- artistic creativity should be developed and supported.