I- Constitutional chromosomal disorders

I-1. Incidence

I-2. Etiology

I-2.1 Genetic factors
I-2.1.1 Chromosomal factors
I-2.1.2 Genetic factors
I-2.2. Parental age
I-2.3. Environmental factors

II- Karyotype indications

II-1. Synopsis
II-1.1 Karyotype
II-1.2 Fluorescent in situ hybrization (FISH)

II-2. Indications
II-2.1. Perinatal period
II-2.1.1. Stillbirth
II-2.1.2. Neonatal period
II-2.1.2.1. triad: dysmorphism, malformation, neurological deficit
II-2.1.2.2. ambiguous genitalia
II-2.2. During infancy and adolescence
II-2.3. In adulthood
II-2.4. In the foetus
II-2.5. Acquired diseases - cancerology

I- Constitutional chromosomal disorders

I-1 Incidence

6 for 1000 births
- gonosomal disorders:2/1000 (of which 1.4/1000 have a male phenotype);
- trisomy 21: 1.5/1000; other unbalanced autosomal disorders: 0.5/1000;
- balanced chromosomal disorders with a normal phenotype 2/1000
- among 1000 known pregnancies 150 will abort spontaneously: among them 100 have an abnormal chromosomal complement: 20 Turner syndrome, 20 trisomies 16 and 20 triploids (more than 10% of each of those 3 syndromes are found among the spontaneous miscarriages); those figures exclude the undetected very early foetal losses (only one out of 2 conceptions would come to term).
- Humans would have the highest rate of abnormal gametes.

I-2. Etiology
I-2.1 Genetic factors
I-2.1.1 Chromosomal factors
The incidence of balanced chromosomal defects is 2/1000; their sibs will have:
- have a normal karyotype,
- a normal phenotype with a balanced chromosomal complement,
- an abnormal phenotype with an unbalanced chromosomal complement.
An aneusomal chromosomal recombination can occur during meiosis; the risk will vary with the type of rearrangement and the sex of the carrier parent.
I-2.1.2. Genetic factors
Unknown but suspected due to the recurrence of trisomy 21 (1 to 2%).
I-2.2. Parental age
Maternal age:
Increased risk of trisomy 21, Klinefelter syndrome (XXY), trisomy 13, trisomy 18, triple X.
However some chromosomal disorders are not linked to maternal age (Turner syndrome, trisomy 16).
Causes of meiotic non disjunction related to maternal age are not well defined:
- degenerative spindle fibers?
- lower chiasma frequency?
- low frequency of sexual intercourse leading to late fertilization of ovocytes?
  • low rejection uterine capacity of abnormal zygotes?
  • exogeneous factors?
I-2.3 Environmental factors
Ovulation induction, ionizing radiations, antimitotic agents.

II-Karyotype indications
II-1. Synopsis
II-1.1. Karyotype
The karyotype is the study of the individual chromosomal complement through which one can detect chromosomal rearrangements constitutional or acquired on at least one band equivalent to $10^3$ to $10^4$ K bases; since the scale is not at the gene level the karyotype is useless in monogenic diseases (except in research).
10% of children with a congenital defect would have a chromosomal anomaly.
Karyotype can be done on peripheral lymphocytes, tumour cells (bone marrow) fibroblasts, gametes, amniocytes or trophoblasts upon indications.
A mitogen stimulates cell growth (lymphocytes), mitoses are blocked in metaphase by a spindle poison, a hypotonic solution will disperse the chromosomes and the banding techniques will reveal a number of successive bands on each chromosome.

II-1.2. Fluorescent in situ hybridization (FISH)
Extemporaneous tissues, cells in culture, fixed tissues, cells embedded in parafin.
Indications:
- Aid to cytogenetic studies.
- Phenotype suggesting a micro deletion in the patient.
- Rule out mosaicism if the phenotype is characteristic of a known syndrome.
- Identification of a cryptic chromosomal aberration if the autopsy does not confirm an abnormal phenotype.
- Follow up of bone marrow transplants when the donor is of the opposite sex.
- Rule out numerical chromosomal anomalies in prenatal studies when the ultrasound examination reveals a number of specific anomalies or screening of foetal tissues in high risk pregnancies for chromosomal non-disjunction.
- Comparative genomic hybridization, multi FISH, DNA probes etc range of valuable techniques complete the classical arsenal of examination.

II-2. Indications
II-2.1. During the perinatal period
II-2.1.1 In a stillbirth
Karyotype on fibroblasts (umbilical cord, lung, muscle) if the etiology in unknown or when one suspects a chromosomal disease (for instance in dysmorphic syndromes and/or visceral anomalies); a complete anatomo-pathological examination is indicated (feto-pathology).
II-2.1.2 During the neo-natal period.
II-2.1.2.1 In any dysmorphic syndrome and/or malformation (s) and/or neurological deficit, unless a known etiology is likely involved (teratogenic embryopathy or monogenic disease).
II-2.1.2.2. In ambiguous genitalia.
Pseudohermaphrodisim
- male (variable karyotype: XY, XY/ X0, etc )
- female (normal karyotype 46,XX).
Gonadal dysgenesis: (variable karyotype: XY, XY/X0), XX/XY, XX/XXX /X0 etc.
True hermaphrodite (variable karyotype: XX, XY, XY/X0, XX/XY, etc). Histology of gonadal tissues will be useful in the differential diagnosis of those syndromes. Karyotype is only one of several elements on which is based the gender choice.

II-2.2. during childhood and adolescence if

II-2.3. during adulthood
Parents of a child with a chromosomal disorder. Sterility workup once gynaecological or endocrine causes have been ruled out (Klinefelter, Turner, Testicular feminization).
If more than two spontaneous miscarriages cytogenetic studies are indicated on the parents to rule out a translocation carrier; a foetal karyotype is recommended if at all possible.

II-2.4. during pregnancy
Tissues: amniotic fluid cells obtained by amniocentesis, chorionic villi, lymphocytes obtained by cordocentesis.
Indications:
- Advanced maternal age
- Previous pregnancy with an abnormal chromosomal complement
- Previous stillbirth with an abnormal chromosomal complement.
Balanced chromosomal rearrangement (translocation, inversion,...) or not (marker, mosaicism, sexual aneuploidy) in one of the parents.
Abnormal maternal serological screening test.
Abnormal foetal ultrasound.
Risk of an unstable chromosomal syndrome
- Confirmation of foetal mosaicism diagnosed earlier during the pregnancy (this procedure has a 1% risk of miscarriage).

II-2.5. Acquired diseases? Cancerology
De novo chromosomal anomalies (on tumour cells) while the constitutional karyotype remains normal (note: although neoplastic diseases are considered as acquired, some have a hereditary component; see: Cancers héréditaires those anomalies are characteristic, often pathognomonic in leukemias and sarcomas: t(9;22) in chronic myelogeneous leukemia, t(3;13)(q35;q14) in the alveolar rhabdosarcoma).
Those anomalies may confirm the diagnosis and help defining the prognosis. However several are identified and most give little insight on solid tumours.
Role of oncogens (ABL in 9q34, MLL in 11q23, ETV6 in 12p13, AML 1 in 21q22), and or tumour suppressor genes (Rb in 13q14, P53 in 17p13) ? in diagnosis.
Tissues: peripheral lymphocytes, bone marrow, lymph nodes, solid tumours, pleural effusion, ascites...
Indications:
Diagnostic
Follow up of the disease: disappearance of the clone under treatment and/or remission, relapse, acute phase.

This article should be referenced as such: