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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 triploidies (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, antimetabolic 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 paraffin
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 etca 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 is unknown or when one suspects a chromosomal disease (for instance in dysmorphic syndromes and / or visceral anomalies); a complete anatomo-pathological examination is indicated (foeto-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

Pseudohermaphroditism

- 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

Psycho motor retardation (fra X, Klinefelter)

Dysmorphism with visceral anomalies undetected during infancy

Unexplained short stature (Turner)

Hypogonadism (Klinefelter, Turner).

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 myelogenous 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 oncogenes (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.

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