Other Constitutional Chromosome Diseases

GENERAL COMMENTS

- **Imbalances concerning** gonosomes are less deleterious than those affecting autosomes; Imbalances leading to an excess of gene dosage (i.e. duplications, trisomies) are less deleterious than those resulting in a deficit (i.e. deletions, monosomies).

- **Bias of sampling**: the most deleterious chromosome imbalances are not seen but result in early miscarriages; miscarriages and stillbirths occur in other syndromes, and only the less deleterious are compatible with life.

- **Some signs are characteristic** of the disease. They are due to a gene effect or to the combination of genes effects. their association can be called a contiguous gene syndrome (see below).

Other signs are aspecific of the region involved; they are the result of general gene imbalance and/or cell division disturbances, and may be found in many chromosome syndromes: growth retardation, microcephaly, mental retardation, low set ears ... can be found in various disease with no gene similarity.

- **Type/contertype**: trisomy 4p syndrome (not herein described) exhibit some signs which are the opposite of del(4p) syndrome (e.g. flat/high forehead, aplasic/large glabella, prognatism/microretrognatism). In trisomy 4p, genes located in 4p are in 3 sets, while in del(4p) these genes are in only 1 set. This is an example of probable gene dosage specific effects.

- **Haploinsufficiency**: is a term used in case of a deleted segment with deleterious effects; it means that the remaining haploid set of gene(s) is insufficient to allow a normal function.

- **Critical region**: it was previously thought that a trisomy phenotype was due to the global excess of the extra chromosome (e.g. trisomy 21), and a deletion syndrome to the haploinsufficiency of the whole deleted segment. With the description of cases with overlapping imbalances, it became clear that some regions of imbalance had more deleterious effects, while others induced only mild disturbances. The critical segment is, in some instances, very narrow: band q22.3 is responsible of most of the trisomy 21 phenotype; it may even be smaller: the 200 kb critical segment in del(4p) syndrome. In the latter case, one has even evoked the notion of "contiguous gene syndrome".

- **Continuous genes syndrome**: some Mendelian inherited diseases have been known for long, and their deleterious effect well described. It has happen that a given patient had presented with the addition of phenotypes from different inherited diseases. A well known example is that of a patient with the addition of Duchenne muscular dystrophy, chronic granulomatous disease, retinitis pigmentosa, and Mc Leod syndrome. This patient had a deletion in Xp21, where all these genes map.
• **Cryptic rearrangements/imbalances:** it is likely that a percentage of chromosome imbalances remain undetected and/or undetectable: some of these imbalances are probably cause of major anomalies; the location of the chromosome imbalance may not be suspected if the phenotype is not reminiscent of a well known syndrome; others cryptic imbalances may have no, or slight effects, and will never be uncovered (another bias of sampling!).

**OTHER AUTOSOMES DISEASES**

**A - DELETION 4p (Wolf-Hirschhorn syndrome / Pitt-Rogers-Dank syndrome)**

- Karyotype: deletion of band 4p16 gives full phenotype; critical segment narrowed to 200 kb.
- Clinics:
  - hypotrophy, low birth weight: 2 kg.
  - microcephaly, high forehead, large glabella, broad nose in prolongation of the eyebrows line: greek helmet aspect.
  - hypertelorism, ocular malformations, hare-lip / cleft palate.
  - long, slender, manicured fingers.
- Malformations:
  - heart (50%).
  - ocular; in particular colobomata (25%).
- IQ = 20; seizures; often bedridden.

**B - DELETION 5p (cri-du-chat syndrome)**

- Karyotype: deletion of 5p14-p15 most often; critical segment narrowed to 5p15.2 (about 2 Mbases); the deletion is de novo in 85% of the patients, and 15% are familial cases of parental balanced rearrangement
- Epidemiology: 0.02 / 1 000 births.
- Clinics:
  - typical high-pitched cry in the newborn (like a kitten)
  - microcephaly, round moon-shaped face, hypertelorism, broad nasal bridge, downward slanting palpebral fissures, and micrognathia; growth retardation
  - triradius axial in t’.
  - hypotonia in the newborn; hyperactivity, tantrums, destructive behaviour is frequent in the adult; autistic-like features may be present; heavy psychomotor retardation (IQ may be at 20).
- Malformations: rare.

**C - TRISOMY 8 MOSAICISM**

- Epidemiology: sex ratio 3M/1F; increased parental mean age.
- Clinics:
  - high forehead, everted lower lip.
discrete dysmorphia.
• dermatoglyphics: deep palmar/plantar furrows.

- Malformations: kyphoscoliosis, hemivertebrae and other osteoarticular disorders.
- I Q: 50 to 70 mainly; however, cases with normal intelligence and no visible malformation remain undetected.

D - TRISOMY 9p

- Karyotype: critical segment likely to be in 9p22-p24.
- Clinics: microcephaly, deeply set eyes, broad nose.
- Malformations: rare.
- I Q = 50.

E - TRISOMY 13 (Patau syndrome)

- I. Epidemiology:
  o 0.1 / 1 000 births.
  o increased parental age.
  o normal pregnancy duration.
  o life expectancy: frequently found in early miscarriages, and in late miscarriages; stillbirths are common, and babies often die in the neonatal period; very few reach adulthood.
- II. Clinics:
  o microcephaly, receding forehead.
  o microphthalmia/anophtalmia, colobomata of the iris, cataract.
  o arrhinencephaly, probocis.
  o hypotelorism.
  o scalp defect (in relation with neural tube fusion defects).
  o hare-lip / cleft palate.
  o umbilical hernia: 1/3 of cases.
  o genitalia: cryptorchidy in the male, uterus bicornis (constant) and vagina duplex (often) in the female.
  o fingers in flexion position; postaxial polydactyly 80 % (hands and feet); club foot; dermatoglyphics: axial triradius in t"; thenar pattern.
- III. Malformations: constant, heavy, leading to early death in most of the cases.
  o Central nervous system:
    ▪ arhinencephaly (50 %).
    ▪ hypoplasia of the corpus callosum (20 %).
    ▪ hypoplasia of the frontal lobe.
    ▪ spina bifida.
  o Ocular:
    ▪ micro/anophtalmia (90 %).
    ▪ coloboma.
    ▪ retinal dysplasia.
    ▪ luxation or absence of lens.
  o Cardiac (constant):
- ventricular septal defect.
- patent foramen ovale.
- persistence of ductus arteriosus
tetralogy of Fallot.
  - Renal (50 %):
    - hydromeophrosis.
    - polykystic kidneys ...
  - Digestive (50 %):
    - malrotation of the intestine.
    - malformation of the pancreas.
    - gallbladder agenesis.
  - Bones:
    - spina bifida.
    - rib malformations.
  - IV. Karyotype:
    - most often free and homogenous trisomy.
    - sometimes translocation t(13q 14q).
    - sometimes mosaic trisomy.

**F - DELETION 18p (Edwards syndrome)**

- brachycephaly, ptosis, broad nose, irregular teeth.
- kyphoscoliosis.
- holoprosencephaly (10%).

- IQ = 50; may have psychiatric behaviour.

**G - DELETION 18q**

- Karyotype: deletion of 18q21-qter most often; critical segment maps to 18q23.
- Clinics:
  - severe hypotonia (frog-like).
  - midface hypoplasia; carp-shaped mouth.
  - tapered fingers.
  - hearing impairment
  - growth retardation
- Malformations:
  - ocular: constant.
  - osteoarticular.
  - genitalia.
  - variable IQ, from 30 to over 70.

**H - TRISOMY 18**

- I. Epidemiology:
o 0.2 / 1 000 births.
o increased parental age.
o pregnancy duration is often prolonged.
o life expectancy: frequently found in miscarriages; stillbirths are common, and babies often die in the neonatal period; very few reach adulthood.

• II. Clinics:
o hydramnios; single umbilical artery frequently.
o low birth weight: 2.3 kg.
o constant sign: hypoplasia of the first branchial arch, which implicates:
  --> low set ears
  --> microretrognatism

 o Pierre Robin syndrome:
  • microretrognathism,
  • cleft palate,
  • glossoptosis.
o microcephaly (40 %), dolichocephaly.
o short neck with excess of skin.
o Faun-like ear.
o short thorax and sternum, making the abdomen looking long.
o hernias: diaphragmatic, umbilical, inguinal.
o cryptorchidism (30 %).
o clubfoot; irreducible flexion of forearms; dysplastic nails, absence of distal flexion crease of fingers; clenched fingers with overlap of the 2nd and 5th onto the 3rd and 4th; dermatoglyphics: frequency of arches.

• III. Malformations: constant, heavy, leading to early death in most of the cases.
o Cardiac: constant.
  • ventricular septal defect.
  • patent foramen ovale.
  • persistence of ductus arteriosus
  • valves anomaly, in particular mitral valve
o Renal (1/3): mostly horseshoe kidney, hydronephrosis, polycystic kidneys, hypoplastics kidneys.
o Digestive: frequent; Meckel, anal atresia; pancreas anomalies.
o Brain
o Bones: spina bifida, hemivertebrae, absence of clavicle.

• IV. Karyotype:
o most often free and homogenous trisomy.
o frequency of doubles aneuploidies and mosaics.

**DYSGONOSOMIES AND RELATED SYNDROMES**

**A - TURNER SYNDROME**
In a few words, Turner syndrome (or Ullrich-Turner syndrome) is a syndrome of growth retardation and impuberism with frequent cardiovascular or renal malformation, normal intelligence, due to a chromosome imbalance: 45, X and variants.

- **I. Epidemiology:**
  - 0.4 /1000 female births (but 20 % of chromosome anomalies found in early miscarriages, i.e. about 10% early miscarriages).
  - due to the loss of the maternal gonosome (a X) in 20-30% of cases, or of the paternal gonosome (a X or a Y) in the remaining 70-80%.

- **II. Clinical ascertainment/examination:**
  The diagnosis can be evoked either:
  - in the newborn (from dysmorphia and/or malformations), or:
  - in the girl (from growth retardation, impuberism).

  **1 - neo-natal form:**
  - prenatal (and postnatal) growth retardation
  - single umbilical artery frequently.
  - Bonnevie-Ullrich (BU) status associating:
    - lymphoedema of hands and feet (tough, non inflammatory, regressive at age 2 yrs).
    - excess of skin and webbed skin on the nucha (pterygium colli). 1/3 of BU are found in Turner syndrome, and 75 % of Turner have a BU In the presence of this symptomatology, a karyotype will be undertaken and (cardiac, renal) malformations will be searched for.

  **2 - in childhood or adolescence:**
  - small size (adult < 1,45 m).
  - triangular shaped face, looks sad.
  - hypertelorism.
  - blepharoptosis.
  - possible epicanthus.
  - downward slanting palpebrale fissures.
  - short neck.
  - pterygium colli in more than half cases.
  - low hair line.
  - high-arched palate.
  - micrognatism.
  - low set hears
o shield chest.
o widely spaced nipples.
o short 4th metacarpal.
o cubitus valgus (increased carrying angle of the elbow).
o radius curvus (Madelung's deformity).
o sinking of internal tibial plateau (sign of Kosowicz in the adult).
o osteoporosis (and fracture increased risk) above 45 yrs.
o multiple pigmented nevi; vitiligo and/or café-au-lait spots.
o risk of keloid scars (surgery only when needed, avoid plastic surgery).
o dermatoglyphics: number of digital crests = 187 - (30 * X) - (12 * Y) (herein = 157).
o hypoplastic nails
o infantile external genitalia.
o hypoplastic uterus.
o amenorrhea and sterility.
o absence of breast development.
o rare pubic pilosity.
o normal or subnormal intelligence; the (slight) cognitive defects are limited to visual-spatial/perceptual abilities, attention, motor function, and nonverbal memory. May be partly due to psycho-social suffering, but also to genetic imbalances and their various consequences (e.g. hormone deficiency).

Malformations:

o cardiovascular (20-30%); aortic coarctation (10-15 %) which may lead to death by dissection or rupture of the aorta; bicuspid aortic valve; left superior vena cava, and other malformations; in the presence of aortic coarctation in a girl, a Turner syndrome must be evoked.
o renal (40-50 %): horseshoe kidney, hydronephrosis...
o congenitally dislocated hip, scoliosis
o sense-organs: deafness (impaired hearing in up to 40%), myopia, cataract, strabismus.
o X linked recessive inherited traits have the same frequency in Turner syndrome and in the male, since they both have only 1 X; this frequency is that of the allele (e.g. daltonism, hemophilia, Duchenne de Boulogne myopathy...).

III. Diagnosis: the karyotype:
o 45, X homogeneous: 55 % of cases.
o isochromosomes: i(Xp), i(Xq); deleted chromosomes: del (Xp), del (Xq);
rings: r(x); mosaicism... --> phenotypes are more or less evocative of Turner syndrome some patients having been fertile.
o most of the phenotypic traits are due to Xp deletion, and only ovarian failure is consistently associated with Xq deletions.

IV. Assessments:
o ovarian failure (sex steroid deficiency and amenorrhea).
o streak gonads (germinal cells regress at the 3rd month in utero; biopsy is not needed).
o impaired glucose tolerance; hypertension (20-30%).
o autoimmune thyroid disease (T4, TSH, thyroid-antibody titer determinations).
o X-rays (skeleton, urinary system, heart).

V- Differential diagnosis:
o other disorders with Bonnevie-Ullrich status.
o gonadic dysgenesia.
o other disorders with primary amenorrhea; e. g.: XY females (sex reversal).

VI. Treatments:
o surgery of malformations.
o gonadectomy if a Y chromosome is present in mosaic (neoplastic risk).
o growth hormone and oestrogens to manage growth failure and to induce
menarch and secondary sexual characters and menarch and to prevent
osteoporosis.
o psychological support (sterility).

Comments: Genes implicated in the syndrome are thought to be localised in
the region of the gonosomes which escape X inactivation; the various
clinical manifestations may either be due to haploinsufficiency of specific
genes (in the pseudoautosomal region of X), aneuploidy effects (e.g. on
meiosis), and/or fetal suffering from the lymphoedema.

B - KLINEFELTER SYNDROME

In a few words, Klinefelter syndrome is a syndrome of a normal or gynecoid male
with normal intelligence or mild retardation, infertility, and possible behaviour or
psychiatric problems, due to a chromosome imbalance: 47, XXY and variants.

I. Epidemiology:
o 1.5 /1 000 male births.
o increased maternal age.
o the extra X comes more often from the mother.

II. Clinical ascertainment/examination:
o wide variability in clinical expression:
o rarely diagnosed in childhood (from mental retardation or non specific
anomalies of genitalia),
o more often at puberty (from gynecomastia, small testes),
o or when consulting for infertility.
o physical aspect is often normal,
o they may present with tallness and macroskelia,
o or with gynecoidy (gynecoid obesity: 25 %; gynecomastia: 15-25 %; bi-
trochanteric diameter > bi-acromial diameter).
  • normal penis.
  • small, indolent testes.
  • normal or rare, feminine shaped pubic pilosity.
  • libido diminished; impotence at age 30 yrs is frequent.
  • sterility.
  • normal or moderately delayed intellectual development.
- dyslexia/dysphasia and frontal-executive dysfunction.
- psychiatric behaviour is not rare.
  - 50-fold increased risk of developing breast cancer as compared to normal males (and 8 times less than in females, as the women’s risk is 400 times that of men) (nearly 10% of breast cancers in males are found in Klinefelter patients).

**III. Diagnosis: the karyotype:**
  - 47 XXY homogeneous: 80% of cases.
  - XXXY, XXXXY, XYYY: 10%.
  - in mosaic: 5-10% (may rarely) be fertile.

**IV. Assessments:**
  - high gonadotropins and low testosterone plasma levels.
  - azoospermia in most non-mosaic cases; however, intratesticular residual foci of spermatogenesis may occasionally be found, and mature spermatozoa may permit paternity using intracytoplasmic sperm injection.
  - biopsy (not needed): seminiferous tubes atrophy, Leydig hyperplasia.

Treatment: testosterone replacement therapy to correct androgen deficiency and to provide virilization; can also have positive effects on mood and self-esteem.

**C - FRAXA and FRAXE SYNDROMES (Fragile Xq or fra(X)(q28))**

**I. Epidemiology:**
  - FRAXA: 0.2 / 1 000 male births and 0.1 / 1 000 female births.
  - FRAXE: 0.02 / 1 000 male births.

**II. Clinics:**
  - the face reminds of the one found in trisomy 8.
  - macrocephaly.
  - high forehead.
  - midface hypoplasia.
  - large nasal root.
  - prognathism.
  - thick lips.
  - high palate.
  - large, unfolded ears.
  - macroorchidy.
  - fertility is often normal.

**III. Mental development and psychiatric behaviour (paragraph written by Denis Reserbat-Plantey):**
  - In the male:
    - Mental retardation is mild to severe (mean IQ = 50): from a delay in school training to the impossibility to acquire writing and reading skills. The Fragile Xq young child is often hypotonic; in the more severe forms, a psychomotor delay is already present (delay in walking...).
- Speech difficulties: delay language appearance, dysarthria, omissions, mumblings, echolalias (tendency to repeat the same sentences and to ask the same questions).
- Behaviour problems: anguish, attention deficit, hyperactivity, impulsiveness, escape of glance, resistance to change, aggressiveness, self-mutilation, stereotypies (wings beating, "flapping") and oddities. Sometimes all these symptoms are present, and constitute an autistic syndrome.
- The various studies carried out among the autists show that 5 to 7% autists are Fragile Xq.
  - In the female:
    - The mental retardation is mild or absent. They can present with: school difficulties (less than in the boy), memory disorders, changing mood, timidity, relational difficulties, and depressive tendency. These symptoms are often misinterpreted for social causes.

IV. Diagnosis: the karyotype can show recurrent gaps in Xq27-q28; however, the diagnosis now rely on the molecular study of the genes.

FRAXA

- The disease is due to the hyperexpansion of a CGG trinucleotide repeats in the 5' untranslated region of the gene FMR-1 (fragility, mental retardation), located in Xq27.3.
- As a consequence of their hyperexpansion, these CpG islands become hypermethylated, leading to shut down the FMR-1 gene expression.
- The normal FMR-1 product is a protein called FMRP, a RNA binding protein widely expressed, in particular in the brain and the testis.
- In the normal population, the CGG repeat size is variable, from 6 to 54 repeats; it is inherited in a stable manner.
- Some people have between 60 and 200 repeats; this is called premutation; it is inherited in an unstable manner (you tend to have more repeats than Mummy), but stable in the individual (identical in each cell). Premutation carriers have a normal phenotype. Frequency of premutations in the population is 2.5/1000.
- Hyperexpansion of more than 200 repeats are called full mutation; they are hypermethylated (on cytosines; even on the active X); it is inherited in an unstable manner, but also, the mutation is unstable in the individual (somatic mutations). Almost all males and half of females with the full mutation exhibit the syndrome. It is milder in females.

Notes:

- passage from the normal allele to premutation as never been observed.
- passage from premutation to mutation (unstability, or expansion through inheritance) is only through transmission from a female carrier.

FRAXE

Atlas Genet Cytogenet Oncol Haematol 2000; 4
- locus in Xq27-q28, 600kb distal to FRAXA.
- Identical process of hyperexpansion of CpG islands.
- much milder phenotype.

Note: this type of unstable mutations has been found in other diseases, such as Huntington disease, a progressive neuropsychiatric disorder with CAG repeats in 4p16.

D - 47, XXX

- Epidemiology: 1 / 1 000 female births; increased parental age.
- Clinics:
  - often undetected: a normal female with normal phenotype, puberty, fertility, and offspring (most often).
  - precocious menopause.
  - mild mental delay and/or psycho-social disturbances are sometimes found.

E - 48, XXXX and 49, XXXXX

- mimics trisomy 21; mental retardation.

F - 47, XYY

- Epidemiology: 1 / 1 000 male births.
- Clinics:
  - often undetected: a normal but tall male with a normal phenotype.
  - fertility may be reduced; normal offspring.
  - mild mental delay can be present; impulsivity, violence, and psychiatric behaviour are not rare.
**G - XX MALE SYNDROME**

- Epidemiology: 0.1 / 1 000 male births.
- Clinics: Klinefelter like phenotype; sterility.
- Sex reversal can be due to the presence of male determining sequences on a X chromosome (from a X/Y interchange at paternal meiosis), or on an autosome (from a Y/autosome translocation in the father), in particular SRY (Sex determining Region, Y chromosome). Other sex determining genes, usually sitting on gonosomes or on autosomes are likely to be involved.

**H - XY FEMALE SYNDROME**

- Epidemiology: 0.1 / 1 000 female births.
- The phenotype is that of a female with ovarian failure, and with or without other stigmata (e.g. sexual anomalies, limbs anomalies).
- Sex reversal in XY females can be due to mutations in SRY in 15%, or to other known or unknown genes mutations; some of these genes map to autosomes (e.g. SOX9 on chromosome 17).

**I - NOONAN SYNDROME**

- formerly called Turner syndrome with a normal karyotype (46, XX or 46, XY) from the shortness and other common signs: this is why it is herein cited. It is in fact an autosomal dominant trait.
- cardiac malformations, mild mental retardation, infertility or fertility.
- a gene maps in 12q24.

**OTHER CHROMOSOME IMBALANCES**

**A - TRIPLOIDY**

- Epidemiology: the most frequent chromosome aberration in early miscarriages; found in 20 % of spontaneous miscarriages. Stillbirths are also frequent; livebirth can occur, but the baby dies shortly afterwards.
- Karyotype: 3N = 69 chromosomes: i.e. 69, XXX, or 69, XXY, or rarely 69, XYY; due to a fertilisation anomaly: digyny: non-expulsion of the 2nd polar body; or diandry: fertilisation of 1 oocyte I by 2 spermatozoa. Diandry is 4 times more frequent than digyny.
- Clinics: Preeclampsia; large placenta, with frequent hydatiform mole; severe growth retardation; microcephaly; syndactily; heavy brain, heart, kidney and ocular malformations leading to death.
B - TETRAPLOIDY

4N = 92 chromosomes. Found in 5 % of miscarriages. Literature records very few live births, but with death soon after.

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