Genetic diseases

Dr. Raghad Hanoon LEC.3

3. Diseases arising from chromosomal abnormalities, (Cytogenetic disorders):

Result from alterations in the number or structure of chromosomes and may affect autosomes or sex chromosomes.

1:200 newborn infants have some form of chromosomal abnormalities, 50% of first trimester abortion is due to chromosomal abnormalities.

Before discussion of chromosomal aberrations, it is appropriate to review karyotyping as the basic tool of the cytogeneticist.

Karyotype is a paragraphic representation of a stained metaphase spread in which the chromosomes are arranged in order of decreasing length.

A variety of techniques for staining chromosomes has been developed. With the widely used Giemsa stain (G banding) technique, each chromosome set can be seen to possess a distinctive pattern of alternating light and dark bands of variable widths

How to write a karyotype?

1. The number of chromosomes
2. The gender
3. Chromosomal disorders if present

Numerical abnormalities:

Are defined as a gain or loss of one or more chromosome(s) whether an autosome or a sex chromosome.

The normal chromosome count is **46 (2n =46)**; an exact multiple of the **haploid number (n)** is called **euploid (normal state).**

Chromosome numbers such as **3n and 4n** are called **polyploidy** (Incompatible with life); generally, results in a spontaneous abortion.

Any number that is not an exact multiple of the haploid (n) is **Aneuploidy (e.g. 47 or 45).**

Most common cause of Aneuploidy is nondisjunction (attach) of either a pair of homologous chromosomes during meiosis I or failure of sister chromatids to separate during meiosis II.

The resultant gamete will have either an extra chromosome (n+1) or one less chromosome (n-1).

Fertilization of such gametes by normal gamete will result in two types of zygotes:

Trisomic with extra chromosome (2n+1) (e.g. Down's), or monosomic (2n-1) (e.g., Turner's).

Monosomy involving an autosome is incompatible with life, whereas monosomy involving sex chromosomes & trisomy's of certain autosomes is compatible with life.

Mosaicism: term used to describe the presence of two or more populations of cells in the same individual (normal cells and monosomy or trisomy cells) Mosaicism affecting sex chromosomes is common while autosomal is much less frequent.
Mosaicism is caused by an error in cell division very early in the development of the unborn baby

Examples of mosaicism include:

- Mosaic Down Syndrome
- Mosaic Klinefelter Syndrome
- Mosaic Turner Syndrome

Structural abnormalities:
In this case, the cell has a normal number of 46 chromosomes but they are morphologically or structurally abnormal.
Structural abnormalities usually result from chromosomal breakage followed by loss or rearrangement of material.

They are of different types as follows:

1. Translocation: Transfer of a part of one chromosome to another chromosome. The process is usually **Regular balanced *(reciprocal)*** translocation when fragments are exchanged between two different chromosomes. A special pattern is called **centric fusion type or *Robertsonian* translocation** involving two acrocentric chromosomes, typically the breaks occur close to the centromere, transfer of the segment lead to one very large chromosome & one small, the short segments are lost & the carrier has **45** chromosome, such loss is compatible with life, because the short arms of all acrocentric chromosomes carry highly redundant genes, but **difficulties arise during gametogenesis**, resulting in the formation of unbalanced gametes that could lead to abnormal offspring.

2. Isochromosomes: result when the centromere divides horizontally rather than vertically. One of the two arms of the chromosome is then lost, and the remaining arm is duplicated, resulting in a chromosome with only two short arms or two long arms.

3. Deletion: involve loss of a portion of a chromosome, single break may delete a terminal segment.
Two interstitial breaks with reunion of the proximal &distal segment may result in loss of intermediate segment, the isolated fragment almost never survive.

4. Inversion: occur when there are two interstitial breaks in a chromosome &the segment reunites after a complete turnaround. Since there is no loss or gain of chromosomal material, inversion carriers are normal.

5. Ring chromosome: is a variant of deletion, after loss of segments from each end of the chromosome, the arms uniting to form ring.

Cytogenic disorders involving autosomes:

Trisomy mainly (21, 18, 13).

- **Trisomy 21 (Down syndrome):**

Is the most common of the chromosomal disorders
About 95% of affected persons have trisomy 21, so their chromosome count is 47.
The most common cause is **meiotic non disjunction, with nondisjunction, a gamete (i.e., a sperm or egg cell) is produced with an extra copy of chromosome 21; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embyo now has 47 chromosomes, with three copies of chromosome 21;** the parents are normal but maternal age has a strong influence on the incidence of Down syndrome (in women more than 45years,1:25 birth).
In 4%, the **extrachromosomal material** is present as a translocation of the long arm of chromosome 21 to chromosome 22 or 14.
1% is mosaicism with **mixture of 46 &47 chromosome.**
Clinical features:
Mental retardation.
Epicanthic folds &flat facial profile.
Abundant neck skin.
Simian creases.
Congenital heart defects &is the principle cause of death in addition to serious infection.
Umbilical hernia.
Intestinal stenosis.
Hypotonia.
Gab between first &second toe.
Predisposition to leukemia.

Trisomy 13 (Patau syndrome):
Clinical features:
Microcephaly &mental retardation.
Microphthalmia.
Cleft lips &palate.
Cardiac defects.
Umbilical hernia.
Renal defects.
Polydactyly.
Rocker-bottom feet.

Disorders involving sex chromosomes

Imbalances in sex chromosomes are more common than autosomal imbalances, because they are typically better tolerated duo to two factors:
(1) lyonization of X chromosomes (Lyon hypothesis) proposed that in females, only one X chromosome is genetically active. X inactivation occurs early in fetal life &called Barr body.
(2) The small amount of genetic information carried by the Y chromosome (Extra Y chromosome readily tolerated because the only information carried by it is related to male differentiation).
Described briefly next are two disorders, Klinefelter syndrome and Turner syndrome, that result from abnormalities of sex chromosomes.

- **Klinefilter syndrome:**

Defiend as a male hypogonadism develops when there are at least 2 X chromosome &one or more Y chromosome.
Karyotype: most patients are 47,XXY in 80% and mosaic in 20%.
Causes:
Advanced maternal age.
History of irradiation of either parent.
Clinical features:
Hypogonadism
Marked testicular atrophy, Gynecomastia.
Reduced facial &body hair (failure of male secondary sexual characteristics development)
Increase length between the soles &the pubic bones (elongated body).
Decrease serum testosterone level.
Some with mental retardation
The principle clinical effect is **sterility;** only rare patient is fertile.
Histologically:
Hyalinization of tubules which appear as ghost like in contrast lydig cells are prominent.

- **Turner syndrome**

Characterized by hypogonadism in phenotypic female result from partial or complete monosomy of X chromosome.
Karyotype: 45 XO.

Clinical features:
Short stature.
Low posterior hair line.
Cubitus vulgus (increase in carrying angle of the arms).
Shield like chest with widely spaced nipples
High arched palate.
Lymphoedema of the hands &feet.

Variaty of congenital malformation e.g. horseshoe kidney, coarctation of aorta.
Failure of development of secondary sexual characteristics.
Genitalia remain infantile (little pubic hair, primary amenorrhea.
Ovaries fibrosed which is devoid of follicles.
Decrease ovarian estrogen level.