

PEDIATRICS

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GENETICS DISORDER

Chromosomal disorders

Each human normally has 22 pairs of autosomes & 1 pair of sex chromosomes (XX in female & XY in male). Chromosomal diseases result from either numerical or structural abnormalities of chromosomes. The general incidence of chromosomal diseases is about 5/1000 (0.5%). The recurrence risk is low (<1%).

Multifactorial disorders

These disorders are caused by a combination of genetic liability & environmental factors. The general incidence of most multifactorial disorders is about 1/1000. The recurrence risk is about 2-5% & it is higher when the defect is severe. Examples of multifactorial disorders are birth defects (congenital heart diseases, neural tube defects, cleft lip, cleft palate, pyloric stenosis) & midlife disorders (hypertension, DM, coronary heart diseases, hyperlipidemia, peptic ulcer).

Single gene disorders

There are over 3000 different single gene disorders, fortunately, most of them are rare. The recurrence risk depends on the mode of inheritance which can be autosomal recessive, autosomal dominant, or X-linked. Generally, the recurrence risk is very high (25-50%). Examples of single gene disorders are metabolic diseases (aminoacids, carbohydrates, lipids, mucopolysaccharidosis) & systemic diseases (blood, renal, endocrine, neurological, & skeletal diseases).

Autosomal recessive disorders

The mutant gene is carried by both asymptomatic parents to affect 25% of their children. So, the recurrence is 25%. This mode of inheritance has a strong relation to consanguineous marriage. Examples are (galactosemia, cystic fibrosis, Wilson disease, Werdnig-Hoffman disease, ataxia telangiectasia & adrenal hyperplasia).

Autosomal dominant disorders

The mutant gene is usually carried by a one diseased parent to affect 50% of his or her children. So, the recurrence risk is 50%. It is important to mention that several autosomal dominant diseases represent a new mutations & appear in children of normal parents. Examples are (congenital spherocytosis, achondroplasia, neurofibromatosis, Huntington chorea, hypercholesterolemia & polycystic kidney).

X-linked disorders

The mutant gene is carried by the asymptomatic mother to affect 50% of her sons. So, the recurrence risk is 50% of male offsprings. The mother also transmits the trait to 50% of her daughters to be carriers(as their mother). Examples are(G6PD deficiency, hemophilia A& B, fragile X syndromes, Duchenne muscular dystrophy & color blindness).

Accurate diagnosis of genetic disorders is important for 3 reasons:

1. for the patient: some genetic diseases can be largely controlled by:
 - ✓ Simple dietetic measures: As in phenylketonuria & galactosemia.
 - ✓ High vitamin therapy: As in homocystinuria.
 - ✓ Avoidance of exposure: As in G6PD deficiency.
 - ✓ Drug therapy: As in Wilson disease.
2. for siblings: Early diagnosis can be made.
3. for parents: Precise genetic counseling can be offered.

CHROMOSOMAL DISORDERS

Chromosomal disorders are either due to :

1.Numerical abnormalities:

A. Autosomal chromosomes(triosomies & monosomies).

B. Sex chromosomes(triosomies & monosomies).

2. Structural abnormalities (deletion, translocation & inversion).

Accurate clinical diagnosis of chromosomal disorders can be very difficult even to experts. Although some chromosomal disorders have a quite peculiar features & can be easily recognized, most other disorders do not present with a clear characteristic features. Moreover, several single gene disorders & morphological syndromes can present with clinical features that can be easily confused with chromosomal disorders. It is very essential to know how to suspect a chromosomal disorder. It is important to realize that abnormal facial features are not peculiar to chromosomal diseases & they can be caused by several genetic & even nongenetic diseases.

Chromosomal analysis

Once a chromosomal disease is suspected, chromosomal analysis is indicated for confirmation or exclusion. Study of chromosomes can be performed on any tissue in which cells are actively undergoing mitosis.

1.Peripheral blood study

It is the most commonly used study because blood is the easiest tissue to obtain. The T-cells are stimulated to enter mitosis. Result of analysis can be obtained after 4-5 days(the time required by the cells to enter

metaphase).

2. Bone marrow study

As bone marrow cells are constantly dividing, the result of analysis can be obtained within 6 hours of obtaining the sample. The main indication of chromosomal bone marrow study is leukemia.

3. Organ tissue study

Tissue biopsies (usually the skin) can be used for chromosomal studies when blood sample can not be obtained (as in case of stillbirth) or when the diagnosis of mosaicism need to be confirmed. The results of analysis can be obtained after, at least, 3-4 weeks (the time needed for the cells to grow in culture).

Chromosomal karyotype

is the term used for the "arrangement of chromosomes that is made from the photomicrograph". This arrangement allows the analysis of chromosome number & structure. The chromosomes are arranged in 7 groups (A to G) in order of decreasing size.

COMMON AUTOSOMAL DISORDERS

1. Trisomy 21 (Down syndrome)

It is the most common autosomal trisomy (1/700 livebirth). It has 3 genetic patterns; nondisjunction (95% of cases), translocation (4%), & mosaicism (1%). The incidence of Down syndrome raises dramatically with advanced maternal age (1/2000 at age 20, 1/1000 at age 30, 1/100 at age 40, & 1/50 at age 45). The recurrence risk is about 1% above the age-related risk. Clinical recognition of Down syndrome is not difficult even at birth. Characteristic dysmorphic features include hypotonia, flattened occipit, upward slanting palpebral fissures, epicanthal folds, flat nasal bridge, malformed ears, protruded tongue, short, broad hand, Brushfield spots of iris (75%, 7% of normal newborns), simian crease (45%, 5% of normal newborns), hypoplasia of middle phalanx of 5th finger & big space between first & second toes. The most constant features are the upward slanting of palpebral fissures & the big space between first & second toe (present in about 97% of cases). Associated congenital anomalies include congenital heart disease (40-50%) & GIT anomalies (as duodenal atresia), cryptorchidism, cataract, strabismus, congenital hypothyroidism (2%), hearing loss & leukemia (20 times commoner). Delayed motor development & mental retardation (mean IQ is 50) appear in infancy & the intelligence deteriorates during adulthood with increased incidence of Alzheimer disease.

2. Trisomy 18 (Edward syndrome)

It is the second most common autosomal trisomy (1/4000). There is also a relation with advanced maternal age but it is less marked than that of Down syndrome & trisomy 13. Characteristic dysmorphic features include low birthweight, microcephaly with prominent occipit, low-set malformed ears, micrognathia, clenched fist & rockerbottom feet. Associated congenital anomalies include severe CNS malformations with

severe mental retardation, congenital heart diseases(in 60% of cases) & developmental dysplasia of hip. Prognosis is extremely poor. 30% of patients die in neonatal period & 90% die in infancy.

3.Trisomy 13(Patau syndrome)

It is the third most common autosomal trisomy(1/6000). There is also a relation with advanced maternal age but it is less marked than that of Down syndrome. Characteristic dysmorphic features include low birthweight, microcephaly, coarse features(low anterior hair line, microphthalmia, hypotelorism, median cleft lip & palate), low-set malformed ears, polydactyly & rockerbottom feet. Associated congenital anomalies include severe CNS malformations(including holoprosencephaly) with severe mental retardation, congenital heart diseases(80% of cases) & genital malformations. Prognosis is extremely poor. 50% of cases die in neonatal period & 90% die in infancy.

Autosomal deletion syndromes

A deletion syndrome results from a deletion of a part of the short arm(p-) or long arm(q-) of a chromosome. Common features of deletion syndromes include low birthweight, microcephaly, mental retardation & dysmorphic features. An example of deletion syndromes is Cri du chat syndrome(5P-) which presents with features as cat-like cry, round face & antimongoloid slant. Deletion syndromes are not as common as trisomies(1/50,000). The prognosis depends on the associated anomalies.

SEX CHROMOSOME DISORDERS

1.Klinefelter syndrome(47,XXY male)

It is a common chromosomal disorder of male(1/500 newborn male). It usually presents in adulthood with infertility(small atrophic testes, azospermia), tall stature(long legs) & may be gynecomastia. It can be presented as behavior & learning difficulties in childhood. The basic chromosomal disorder is the presence of an extra X chromosome(47,XXY)in 80% of cases. Some have mosaic pattern. The degree of mental affection is related to the number of extra X chromosomes(48,XXX in 3% of cases & 49,XXXX in 1% of cases). Testosterone supplementation may be offered during the pubertal years to limit skeletal disproportion.

2.Poly-Y male(47,XYY male)

It is a common chromosomal disorder of males(1/1000) characterized by aggressive antisocial behavior & difficult personality problems in school years.

3.Poly-X female(47,XXX female)

It is a common chromosomal disorder of females(1/1000) characterized by a minor degree of affection of motor, speech & mental development. The degree of mental affection is related to the number of extra X chromosomes(48,XXXX & 49,XXXXX in less than 2% of cases).

4.Turner syndrome(45, XO female)

It is a common chromosomal disorder of females(1/1,500-2500 liveborn female) characterized by short stature, webbing of the neck, low posterior hairline, small mandible, prominent ears, epicanthal folds, high arched palate, broad chest, cubitus valgus(increased carrying angle), & gonadal dysgenesis(primary amenorrhea). The condition can be suspected at birth when oedema of the dorsum of hands & feet are present. Associated renal anomalies(30%), recurrent otitis media(75%), thyroid diseases(20%) & cardiac anomalies especially coarctation of aorta(20%) may be present. It has 3 genetic patterns; monosomy 45,XO(50%), mosaicism(15%) & others. Intelligence is usually normal but with specific learning difficulties. The short stature is treated with growth hormone & the ovarian dysgenesis by induction of puberty with estrogen.