DIAGNOSIS AND FOLLOW-UP OF COMPLEX CONGENITAL MALFORMATIONS/MENTAL RETARDATION (MRA/MR)

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[Inquadramento diagnostico e follow-up delle malformazioni congenite complesse/ritardo mentale (MRA/MR)]

ABSTRACT

Complex congenital malformations, associated in 30% of cases with mental retardation, recognize different etiologies: environmental causes, mendelian disease, chromosomal abnormalities, imprinted anomalies. Frequently complex congenital disorders are rare diseases. Rare diseases are infrequent pathological conditions (prevalence in the general population of less than 1/2.000 live births1), and often poorly understood. Because of their rarity these morbid conditions often either go undiagnosed or are diagnosed late with a negative impact for both the affected person and the family. The birth prevalence is high (2-4% of all births). The diagnosis is essential to program complex and integrated care interventions (follow-up programs aimed at early detection of any disease associated with different syndromes) and to carry out proper genetic family counseling (risk of recurrence, prenatal diagnosis, detection of heterozygotes etc).

***Key words*:** *Complex congenital anomalies, diagnosis, follow-up.*

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Introduction

The complex congenital malformations are frequently rare diseases. The rare diseases are infrequent and often little known pathological conditions (1/2,000 live-born in the general population[1]). They are often not diagnosed or diagnosed late with the resulting negative consequences for the patient and his/her family. The birth prevalence is high (2-4% of all births). They are characterized by the presence of health problems and/or functional deficits that require multiple medical, psychological and social support[2-6].

The Centers for rare diseases have multidisciplinary teams that take care globally of patients with rare pathologies. They must make diagnoses, organize clinical and psychomotor follow-up programs and offer genetic counseling to the families. The Centers must prepare an assistance plan for each pathology (calendar of clinical and specialized check-ups, rehabilitation program, introduction into scholastic, social and work activities where possible), that involve doctors, structures and the families. The Center staff should organize initiatives, plans and protocols to protect patients with rare pathologies, involving local pediatricians and organizing seminars and meetings both with health personnel and with the families and associations.

There can be several etiological causes: environmental causes, mendelian diseases, chromosomal abnormalities, imprinted anomalies.

Environmental causes

A complete and deep anamnestic evaluation of patient history with special reference to neonatal age when many risk factors (prematurity[7,8], connatal infections[9,10], nosocomial infections[11-14], chemical mediators[15,16], etc…) may play a role in determinig outcome.

Connatal infections

Viral (citomegalovirus, varicella-zoster virus, herpes simplex virus 1 (HSV-1) e 2 (HSV-2), rubella virus, parvovirus B19 (B19V), HIV, HBV, HCV) and toxoplasma connatal infections may be transmitted from mother to child at different times, ranging from in utero transmission, that occur during pregnancy, perinatal transmission, that takes place during delive-ry and postnatal transmission, that is often the consequence of breastfeeding. They are potentially harmful to the fetus or the newborn child since they may result in miscarriage, fetal death, congenital anomalies, intrauterine growth restriction or severe neonatal disease.

Amniotic band sequence (ADAM complex)

Amniotic band sequence is a congenital disorder due to the entrapment of parts of the fetus (usually a limb or digits) in fibrous amniotic bands during pregnancy (constriction rings around the digits, arms and legs; swelling of the extremities distal to the point of constriction (congenital lymphedema); amputation of digits, arms and legs (congenital amputation)[17].

Prematurity

Infants born before 37 weeks gestation are considered premature and may be at risk for complications even later in life (cerebral palsy, sight problems, impaired cognitive skills, hearing defects, behavioral and psychological problems etc.)[18-27].

Drugs during pregnancy

It is better to avoid the use of drugs during pregnancy unless they are really necessary, taking into consideration the potential risks to the fetus (tab.1)[28].

Mendelian disesases

Autosomal recessive disorders

In an autosomal recessive disorder two copies of an abnormal gene must be present so that the disease or trait may develop. Among the autosomal recessive disorders there are congenital metabolic diseases that occur with heterogeneous clinical signs (growth retardation, mental retardation, birth defects or deformities, neurological disorders, convulsions, gastrointestinal disorders etc.), skeletal dysplasias (spondylocostal dysostosis, Jeune asphyxiating thoracic dystrophy, Ellis van Creveld syndrome etc.)[29,30] and multiple malformation syndromes (Klipper-Feil syndrome, Alport syndrome etc.).

DRUG	TERATOGENIC EFFECT
Aminopterin, methotrexate	CNS and limb malformations
Angiotensin-converting enzyme inhibitors	Prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis
Anticholinergic drugs	Neonatal meconium ileus
Antithyroid drugs (propylthiouracil and methimazole)	Fetal and neonatal goiter and hypothyroidism, aplasia cutis (with methimazole)
Carbamazepine	Neural-tube defects
Cyclophosphamide	CNS malformations secondary cancer
Danazol and other androgenic drugs	Masculinization of female fetuses
Diethylstilbestrol	Vaginal carcinoma and other genitourinary defects in female and male offspring
Hypoglycemic drugs	Neonatal hypoglycemia
Lithium	Ebstein's anomaly
Misoprostol	Moebius sequence
Nonsteroidal antiinflammatory drugs	Constriction of the ductus arteriosus, necrotizing Enterocolitis
Paramethadione	Facial and CNS defects
Phenytoin	Growth retardation, CNS deficits
Psychoactive drugs (e.g., barbiturates, opioids, and benzodiazepines)	Neonatal withdrawal syndrome when drug is taken in late pregnancy
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular, and other defects
Tetracycline	Anomalies of teeth and bone
Thalidomide	Limb-shortening defects, internal-organ defects
Trimethadione	Facial and CNS defects
Valproic acid	Neural-tube defects
Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome

Table 1: Drugs with proven teratogenic effects in humans.
(modified from Koren G et al, N Engl J Med 1998, 338 (16):338(16):1128-37)

Autosomal dominant disorders

Dominance in genetics is a relationship between alleles of a gene, in which one allele masks the expression (phenotype) of another at the same locus. Autosomal dominant diseases are characterized by variable clinical expressivity and penetrance and can be transmitted by an affected parent, or more frequently they are related to new mutations. Several complex disabilities are transmitted with an autosomal dominant trait (Trichorhinophalangeal syndrome, achondroplasia, Sotos syndrome, Rubinstein Taybi syndrome, etc..)[31,32].

X-linked disorders

An X-linked character is a character located on the sex chromosome X. Two X chromosomes are present in the individual female (XX) and 1 in the male (XY). In the female only one X chromosome is active, since the other is inactivated (lyonization). Among the complex X-linked disorders we can include the Fragile X syndrome, Rett syndrome, anhidrotic ectodermal dysplasia[33,34] etc.

Chromosomal abnormalities

About 1 in 150 babies are born with a chromosomal abnormality. These abnormalities are caused by errors in the number or structure of chromosomes. Many children with a chromosomal abnormality have mental and/or physical birth defects. Some chromosomal abnormalities result in miscarriage or stillbirth. Among the most frequent chromosomal pathologies there is the Down Syndrome, but in the past few years, the introduction of array-CGH (comparative genomic hybridization) has made the analysis of the human genome and is quickly revolutionizing the definition of molecular diagnostics in patients with "chromosomal" phenotype (intellectual disability, dysmorphic features, congenital anomalies) and normal karyotype (16p11.2 syndrome. 22q11.2 syndrome, 17q21.31 syndrome etc.)[35-40].

Imprinted anomalies

We inherit two copies of every autosomal gene from our parents, one from our mother and the other from our father. Both copies are functional in most of the genes but, in a small subset one copy is turned off in a parent-of-origin dependent manner. These genes are called 'imprinted' because one copy of the gene was epigenetically marked or imprinted in either the egg or the sperm. Thus, the allelic expression of an imprinted gene depends upon whether it resided in a male or female the previous generation. Imprinted expression can also vary between tissues, developmental stages and species[41].

Imprinted genes are susceptibility targets for various human pathologies since their functional haploid state enables a single genomic or epigenomic change to dysregulate their function causing potentially harmful health effects. Imprinting anomalies often appear as developmental and neurological disorders when they occur during early development, and as cancer when they develop later in life. Specifically, imprinting disorders have been linked to Angelman and Prader-Willi Syndromes, Alzheimer disease, autism, bipolar disorder, diabetes, male sexual orientation, obesity, and schizophrenia[42].

Follow-up

Complex congenital disorders have particular characteristics: chronic nature (the lack of effective treatment or, in the best cases, life-long treatment), rarity (difficult and often delayed diagnosis, lack of guide lines), co-morbidity (various associated pathologies requiring multi-specialistic team). The follow-up programs must foresee, on one hand, the main developmental areas (hearing and psychomotor) and, on the other hand, the precocious diagnosis of all the most frequently associated pathologies (both congenital and acquired).

According to the suggestions of the Italian Society of Pediatric Genetic Diseases and Congenital Dysabilities, personalized interventions (individualized treatment plan) are foreseen for each patient with complex congenital disorders:

- global aspects since children with genetic pathologies have the same rights and health needs as other children (vaccinations, precocious prevention measures),
- multidisciplinary aspects since they have problems of various types and nature for which plurispecialist competences (eg. pediatric cardiology, surgery and immune-hematology, child neuropsychiatry rehabilitation, etc) and multidisciplinary ones (eg. pedagogy, psychology, social assistance, etc.) are necessary,
- integrated aspects since the treatment of these pathologies is medical-clinical and must be undertaken in specialized hospitals and on the territory but also of social, rehabilitative, formative and educative interventions,
- participation of medical staff, family members and patients (when possible), because the definition of the priorities and of the meaningful objectives in

the course of time cannot be kept apart from a continuous sharing and negotiation with the family and among the operators and services involved.

Complex congenital disabilities are often rare diseases. If they are often not diagnosed or the diagnosis is delayed the resulting consequences may be negative for the patient and the family. A diagnosis is essential to plan a multispecialistic and multidisciplinary follow-up program for the patient and also to provide genetic counseling to the family.

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