The Journal of Maternal-Fetal and Neonatal Medicine, 2012; 25(S(1)): 25–29

ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767058.2012.664943

informa
healthcare

REVIEW ARTICLE

Congenital malformations

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Congenital malformations are single or multiple defects of the morphogenesis of organs or body districts identifiable at birth or during the intrauterine life. Their global birth prevalence is about 2–3%. Both genetic and environmental factors, as well as their combination in a multifactorial contest, may induce congenital defects. Congenital malformations may be classified on the basis of clinical, etiologic as well as pathogenetic criteria. Relevant diagnostic and therapeutic tools have been progressively improving in the last decades, contributing to a better identification and a reduction of long-term morbidity and mortality of these patients. A correct identification of a congenital defect is the first step in order to offer a helpful genetic counseling to the parental couple. Because of their increasing life expectancy, congenital malformations represent today a major issue in the health services for the amount of resources they need for the requested multidisciplinary assistance.

Keywords: association, blastogenesis, chromosome, counseling, gene, imprinting, methylation, phenotype, sequence, syndrome, uniparental dysomy

Introduction

Congenital malformations are defects of morphogenesis of organs or body districts, identifiable at birth. Their birth prevalence is about 2–3%. Both genetic and environmental factors may induce congenital defects. Diagnostic and therapeutic tools have been progressively improving in last decades, contributing to better identification and reduction of long-term morbidity/mortality. Because of their increasing life expectancy, congenital malformations represent today a major issue for health services regarding the amount of resources they need.

Evidence of congenital malformations at birth begins a complex clinical process targeted to correct diagnostic definition [1,2], clinical and prognostic evaluation, including treatment opportunity and genetic counseling. Most congenital malformation recognize different causes and pathogenetic pathways in spite of an identical phenotypic pattern [3,4]. Therefore, diagnostic process is often long and difficult and may require long-term follow-up including anamnesis, phenotype analysis, imaging and laboratory tests.

On the basis of clinical criteria, major malformations are morphogenetic defects producing function impairment needing medical or surgical treatment; defects not producing function impairment and not requiring medical assistance are minor malformations (birth prevalence <4%) or phenotypic variants (birth prevalence >4%).

On the basis of etiologic criteria (Table I), primary malformations are morphogenetic defects arising from intrinsic errors of developmental process with genetic origin; disruptions (secondary) occur when environmental factors interfere with otherwise normal developmental process, determining a global impairment or specific damages on developmental fields; deformations arise from *ab extrinseco* mechanical compression during fetal development (amniotic bands, twinning, uterine malformations and masses).

On the basis of pathogenetic criteria, in syndromes, all structural defects arise from a single etiologic factor; sequences are characterized by a cascade of dysmorphogenetic processes originated by a starting event inducing a cascade of secondary defects; in associations, different defects are present with higher frequency than random expectancy, without evidence of any etiologic or pathogenetic correlation; dysplasias are structural defects involving specific tissues.

Associations

Genetic or environmental factors may interfere with blastogenetic processes, when embryo is a single developmental field, producing defects in organs and body districts apparently not related each other. Some associations may share a phenotypic overlapping in relation to a common etiologic and pathogenetic mechanisms.

Newborns with VACTERLS association show many of the defects summarized in the acronym (Vertebral defects, Anorectal atresia, Cardiac anomalies, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, Limb defects, Single umbilical artery). VACTERLS association is often sporadic with a low recurrence risk and is more frequent in the offspring of diabetic mother.

Any kind of congenital malformations in offspring of diabetic mother are 2–4 folds more frequent and are inversely correlated with the efficacy of maternal control, particularly in the periconceptional period. Several factors are involved in the pathogenesis (hyperglycemia, hyperglycosilation of proteins, chronic hypoxia, polyglobulia and lactic acidosis) interfering with blastogenesis, inducing abnormalities of the midline structures and symmetric organs. The fetus is usually macrosomic in relation to fetal hyperinsulinemia, sometimes placental microangiopathy may determine growth restriction.

Sequences

Malformation sequences may depend both on genetic as well as environmental factors. Many organs and systems may be contemporarily involved in malformation sequences (Table II).

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Table I. Etiologic classification of congenital malformations.

- Primary (genetic)
  - Chromosomal abnormalities
    - Numeric
      - Polyploidy
      - Polysomy
      - Monosomy
    - Structural
      - Deletions
      - Duplications
      - Insertions
      - Translocations
  - Monogenic
    - Point mutations
      - Nonsense
      - Missense
      - Frameshift
    - Dynamic mutations
      - Triplet amplification
    - Epigenetic regulation
      - Imprinting defects
      - Uniparental disomy
  - Polygenic
- Secondary (environmental)
  - Biologic agents
    - Viruses
      - Cytomegalovirus
      - Rubella
      - Herpes viruses
    - Bacteria
      - Treponema pallidum
    - Parasites
      - Toxoplasma gondi
  - Chemical agents
    - Drugs
      - Antiblastics
      - Anticonvulsants
      - Antibiotics
    - Abuse substances
      - Alcohol
      - Smoke
      - Cocaine
      - Opiates
    - Metabolic conditions
      - Hyperglycemia, hyperinsulinemia
      - Hyperphenylalaninemia
      - Hyperandrogenism
  - Physical agents
    - Ionizing radiations
    - Electromagnetic radiations
  - Vascular disruptions
    - Subclavian artery vascular disruption
    - Twin-twin disruption sequence
  - Mechanical causes (deformations)
    - Amniotic bands
    - Twinning
    - Oligohydramnios
    - Uterine malformations
    - Uterine tumors

Table II. Main malformation sequences.

Name	Developmental field and organs involved
Holoprosencephaly	Precordial mesoderm, prosencephalic vesicle, rinencephalon, orbits, nose, premaxilla
Septo-optic dysplasia	Optic chiasm, hypophysis
Pierre Robin	Jaw bone, oro-pharyngeal region
CATCH 22	IV brachial arch, II and III brachial pouches
Poland	Pectoral muscle, superior limb
Klippel–Feil	Spine
Potter	Kidneys, urinary tract, lungs, limbs, facies
Prune belly	Urinary tract, abdominal wall
Bladder-cloacal extrophy	Peri-umbilical mesoderm
Rokitanski	Muller ducts
Sirenomelia	Caudal mesoderm
Caudal regression	Caudal mesoderm
Premature rupture of amnios	Median axis, limb deformations, facial clefts
Fetal akinesia	Multiple body districts
Twin-twin disruption sequence	Multiple body districts

Pierre Robin sequence is a developmental defect of the jawbone and surrounding oro-pharyngeal region (isolated or part of more complex syndromes) characterized by microretrognathia, retroglossoptosis, cleft palate, swallowing deficit, pharyngeal stenosis and respiratory distress.

Potter sequence originates by absence or severe reduction of fetal urine output secondary to bilateral kidney agenesis or other urinary tract malformations. Urine production deficit determines a constantly empty urinary bladder, anhydramnios and a cascade mechanism responsible for pulmonary hypoplasia, respiratory distress at birth, dismorphic face with flat profile and fetal hypomotility with multiple postural deformations.

Prune belly sequence, named after of the characteristic abdominal appearance, is related to different nephro-urologic defects [5]. Urethral obstruction is responsible for oligohydramnios, backward urine accumulation and parenchymal damage. Hypertrophic and excessively dilated bladder interfere with fetal development of abdominal wall muscles, diaphragm and testicular migration.

Syndromes

The overall incidence of chromosomal abnormalities is estimated of about 1/170 live births. Prevalence at conception is much higher, with high rate of embryo-fetal loss (about 50% of spontaneous abortions carry chromosomal alterations). Numeric aberrations usually have prezygotic origin, if arising from postzygotic errors they are present only in a percentage of cells (mosaics). Structural aberrations occur *de novo* from meiotic rearrangements or may be inherited from one parent, carrying a balanced chromosomal translocation.

Down syndrome (21 trisomy) is the most frequent chromosomal aberration at birth (about 1/700). In most cases (95 %), it is secondary to a maternal meiotic nondisjunction of homologous chromosomes 21. Incidence increases with maternal age at conception. Neonatal phenotype is characteristic: Brushfield spots, upslanting palpebral fissures, epicanthal folds, small nose, small mouth with prominent tongue, flat facial profile, brachycephaly, flat occipital bone, small low-set ears, short neck with redundant skin folds and single palmar crease. Newborns are hypotonic with joint laxity. Organ involvement may include congenital heart

defects, duodenal atresia or stenosis and urinary tract malformations. Edwards syndrome (18 trisomy) newborns show severe prenatal growth restriction, dolicocephaly, prominent occipital bone and low-set dysplastic external ears, jaw hypoplasia, flexed hands with finger overlapping, talipes with rocker-bottom feet. Other malformations are frequent and are responsible for the severe prognosis with high neonatal mortality. Patau syndrome (13 trisomy) newborns show small trigonocephalic skull, aplasia cutis on the scalp, cleft lip and palate, microphthalmia, variable hypotelorism up to cyclopia, postaxial polydactyly/syndactyly, forced flexion of the fingers, plantar convexity. Other organ involvement is frequent. Patients with fully expressed phenotype usually die in the first month of life. Turner syndrome is the most frequent sex chromosome aneuploidy (1/2500), determined by X chromosome monosomy, frequently as mosaic with a milder phenotype. Neonatal diagnosis may be suspected by lymphoedema of hands and feet, nail dysplasia, neck pterygium, large mouth with downturned corners, dysplastic external ears, left heart output defects, prenatal history of cystic hygroma. Clinical phenotype modifies with age and other features become evident (short stature, short neck, cubitus valgus and gonadal dysgenesis). CATCH 22 is an acronym of the main clinical features (Cardiac abnormality, Abnormal face, Thymic hypoplasia, Cleft palate, Hypoparathyroidism) due to a 22q11.2 deletion. Clinical expressivity is variable depending on the extension of deletion and the involved genes [6]. The evidence of neonatal hypocalcaemia and craniofacial dysmorphic features (micrognathia, cleft palate, anteverted nares and low-set external ears) with a conotruncal heart defect and absent thymic shadow at chest X-rays delineates the phenotype.

Monogenic disorders are single gene mutations with mendelian mode of inheritance. Genotype-phenotype correlation is still not defined for many conditions. Each syndrome may be due to different mutations in the same gene or in different genes (genetic heterogeneity). The same mutation may determine different phenotypes (phenotypical variability), even in the same family, in relation to the interference of other genetic and/or environmental factors. In addition, there are some epigenetic factors acting during the differentiation processes which may modify the genic expression, also in relation to the parental origin of the gene (genomic imprinting).

Cornelia de Lange syndrome occurs in 1/10,000 newborns and is usually sporadic, due to *de novo* mutations [7]. Newborns show a typical face (microbrachycephaly, low anterior and posterior hairline, synophrys, small nose with depressed nasal bridge, anteverted nares, long philtrum, "carp" mouth, maxillary prognathism, low-set ears), intrauterine and postnatal growth restriction, hypertrichosis and upper limb anomalies. Additional malformations may be present. Rubinstein–Taybi syndrome is characterized by genetic heterogeneity, about 25 % of patients present mutations or microdeletions in the gene encoding the cAMP response element-binding protein [8]. Main features are microcephaly, frontal bossing, downslanting palpebral fissures, beaked nose, epicanthal folds, strabismus, maxillary hypoplasia, high arched palate, external ear abnormalities, hand and foot involvement on the I axis and hirsutism. Marfan syndrome is determined by heterozygous AD mutations in the FBN1 gene encoding for fibrillin 1 [9]. Newborns show arachnodactyly, long and thin limbs, increased length joint laxity and hypermobility, muscular hypotonia, hernias, pectus carinatum or excavatum. Heart evaluation shows mitral valve prolapse and aortic defects. Ocular signs (ectopia lentis, early glaucoma) become evident with age. Noonan syndrome is a relatively frequent (1/2000) condition due to AD mutations in PTPN11 gene [10]. Newborns show hypertelorism, upslanting palpebral fissures, low-set posteriorly rotated ears, neck pterygium, shield chest with deformation of the sternum, lymphoedema. Heart involvement is at the level of pulmonary output. Prader–Willi syndrome is determined by absent expression of genes with paternal origin in the region 15q11-q13, arising from microdeletions of paternal chromosome 15 or maternal uniparental disomy (UPD). Methylation test may identify almost all patients. Newborns show congenital hypotonia, respiratory and feeding difficulties (tend to improve after the neonatal period), hypomimic face, genital hypoplasia [11]. Beckwith–Wiedemann syndrome is determined by an altered balance between cooperative genes in the region 11p15 involving imprinted genes encoding for growth factors and receptors. Main neonatal features are exomphalos, macroglossia and gigantism. Other signs are visceromegaly, adrenocortical cytomegaly, auricular indentations, hypoglycemia and limb hemihypertrophy. There is an increased risk of malignant tumors (Wilms tumor, adrenal carcinoma and hepatoblastoma). Silver–Russell syndrome is a sporadic condition with genetic heterogeneity involving imprinted genes [12]. Phenotype is characterized by prenatal and postnatal growth restriction with normal development of the skull (pseudohydrocephalic appearance), craniofacial features (triangular shaped face and broad forehead), body asymmetry and minor malformations. Goldenhar syndrome is a spectrum of malformations involving eye, ear and vertebrae (hemifacial microsomia, ipsilateral deformity of the external ear, epibulbar dermoid, coloboma of the upper eyelid, cervical vertebrae defects) with heterogeneous etiology and highly variable phenotype [13]. Its defects are more often unilateral and origin from a vascular disruption of branchial arches. Smith-Lemli-Opitz syndrome is a rare autosomal recessive (AR) condition, caused by mutations in the steroid-delta-7-reductase gene [14], determining a severe deficit of endogenous cholesterol and its derivatives. Newborns show intrauterine growth restriction, severe hypotonia, microdolicocephaly, micrognathia, hypovirilization and many other features. Failure to thrive and psychomotor delay worsen with age.

Disruptions

Congenital malformations can be secondary to exogenous factors acting during intrauterine life (Table I), inducing abnormalities of developmental processes. Etiologic identification (Table III) is important to offer genetic counseling and estimate recurrence risk in the family. High IgM level soon after birth may strongly predict fetal infection. Any substance introduced in the human organism (drugs, alcohol, smoking, abuse substance) or produced by maternal metabolism in specific situations may cross placenta, reach the fetus and be dangerous for embryo-fetal development. Individual and placental metabolism may largely influence clinical effects, dosage and timing of administration.

Any vascular accident at early stages of the embryo-fetal development may determine subsequent morphogenetic defects in the related body districts. Poland sequence includes pectoral muscle agenesis and ipsilateral superior limb reduction defects. Twin-twin disruption sequence is related to the intrauterine developmental impairment of a monozygotic twin involving several structures (brain, brachial arches, limbs, gut and kidneys).

Table III. Main disruptions determined by biologic and chemical agents.

	Phenotype
Biologic agent	
Cytomegalovirus	Microcephaly, intracranial calcifications, psychomotor delay, sensorineural hearing loss, chorioretinitis, hepatosplenomegaly, thrombocytopenia, virus presence in secretions and biologic fluids (urine)
Rubella virus	Microcephaly, psychomotor delay, congenital cataract, sensorineural hearing loss, heart defects, hematologic alterations (anemia, thrombocytopenia)
Varicella-Zoster virus	Mental retardation, cortical atrophy, seizures, chorioretinitis, skin scars
Treponema Pallidum	Palmoplantar pemphigus, exanthema with skin scars, anemia, thrombocytopenia, hepatosplenomegaly, miocarditis, chorioretinitis, muco-haematic rhinitis, skeletal alterations (lacunae, caput quadratum, metaphyseal ossification defects, osteochondrites and secondary pseudoparalises)
Toxoplasma Gondi	Hydrops, hydrocephalus, intracranial calcifications, chorioretinitis, cataract, seizures, hepatosplenomegaly, skin rush
Chemical agent	
Anticonvulsant drugs	Cleft lip and palate, neural tube defects, congenital heart defects
	Hydantoin (microcephaly, mental retardation, CNS abnormalities, small nose, facial bone hypoplasia, epichantus, hypertelorism, strabismus, cleft lip and palate, micrognathia, short neck, heart defects)
	Trimethadione (microcephaly, facial bone hypoplasia, palpebral synophrys, epichantus, external ear dysplasia, urogenital defects, heart defects)
	Valproic acid (trigonocephaly, reduced bitemporal diameter, facial bone hypoplasia, small nose, cleft lip and palate, urogenital and limb defects)
Alcohol	IUGR, peculiar face (microcephaly, short palpebral fissures, small nose with anteverted nares, hypoplasic nasal philtrum, microretrognathia), neurologic abnormalities (hypotonia, seizures, poor motor coordination, mental retardation)
Cocaine	Prematurity, IUGR, microcephaly, urogenital and skeletal malformations
Heroin	IUGR, low birth weight, congenital malformations
Maternal diabetes	Macrosomia, hypoglycemia, hypocalcaemia, ventricular septal hypertrophy, caudal dysgenesis, any kind of congenital malformations (skeletal, cardiac, renal, intestinal, CNS...)
Maternal hyperphenylalaninemia	Defects of cellular proliferation and migration with myelinization delay (IUGR, severe microcephaly, hypotelorism, prominent nose, low-set dysplastic external ears, mental retardation, cleft lip and palate, conotruncal heart defects)

Dysostoses

It is a heterogeneous group of birth defects with skeletal involvement, due to mutations of genes involved in bone development. Classification is based on phenotypic or genetic criteria. Most conditions are determined by mutations in fibroblast growth factor receptor (FGFR) genes, with string evidence of genetic heterogeneity and genic pleiotropism. Genotype/phenotype correlation is difficult and can be influenced by other genes (epistatic) as well as other interactive cytoplasmatic and environmental factors.

Craniofacial dysostoses

Craniosynostoses depend on precocious closure of cranial sutures that limits cranial growth, producing a deformation of the skull depending on suture involvement (kind, timing, extension and symmetry). There are many conditions characterized by not-syndromal craniosynostoses. Scaphocephaly depends on the precocious closure of the sagittal suture with consequent restriction of growth along transverse axis and compensatory growth excess along antero-posterior axis. Plagiocephaly depends on the precocious closure of only one coronal suture with consequent ipsilateral growth restriction and flattening of frontal bone. Brachycephaly depends on the precocious closure of both coronal sutures with consequent growth restriction along antero-posterior axis and compensatory skull development in height. Acrocephaly depends on the precocious closure of coronal and sagittal sutures with consequent severe growth restriction along both antero-posterior and transverse axes and compensatory development in frontal region. Trigonocephaly depends on the precocious closure of metopic suture with a longitudinal bone crest in median frontal region, determining a triangular appearance of the skull. Cloverleaf skull is related to the precocious closure of coronal, sagittal and lambdoideal sutures with excessive skull growth in height and bilaterally determining a trilobar appearance. In other newborns, it is possible to recognize a specific condition of syndromal craniosynostosis. Apert syndrome newborns show acrocephaly (synostosis of coronal sutures), frontal bossing, flat occipital bone, exophthalmus, hypertelorism, small upturned nose, maxillary hypoplasia, low-set ears and syndactyly of hands and feet (spoon shaped hand with bone and nail fusion) due to AD *de novo* FGFR2 mutations [15]. Crouzon syndrome is the most frequently reported syndromal craniosynostosis characterized by acrocephaly (synostosis of coronal sutures), frontal bossing and flat occipital bone, ocular proptosis, small upturned nose, maxillary hypoplasia, with no hand and foot involvement, due to AD FGFR2 mutations. Muenke syndrome is a common unilateral coronal craniosynostosis with brachydactyly, determined by a AD Pro250Arg FGFR3 mutation [16]. Pfeiffer syndrome is a rare acrocephalosyndactyly with ocular proptosis, maxillary hypoplasia, low-set ears, cloverleaf skull, hand and foot I ray hypoplasia, determined by several AD mutations in FGFR1 and FGFR2 genes.

Other craniofacial dysostoses are Treacher-Collins syndrome characterized by a developmental defect of jaw and facial bones, with wide variability, determined by several different mutations in the gene codifying for the treacle protein, which has a key role in the early craniofacial development [17]; Nager syndrome, a sporadic condition with genetic heterogeneity characterized by mandibulofacial dysostosis with associated preaxial limb abnormalities; Klippel–Feil anomaly, a developmental defect of the spine, with possible alterations at cervical, thoracic and lumbar level (short neck, pterygium, kyphosis and scoliosis); and limb dysostoses, digital defects of one or more contiguous bones, whose development pathway is determined by a complex genetic

system, phylogenetically common to most of vertebrates (polydactyly, syndactyly, symphalangism, brachydactyly, ectrodactyly and oligodactyly).

Osteochondrodysplasias

It is a wide and heterogeneous group of genetically determined conditions, involving the development of osseous and cartilaginous tissues. Their overall prevalence at birth is about 1/5000, secondary to a sensible reduction in the last decades with prenatal diagnosis for most severe conditions. Classification is based on phenotypical evidences, modified by the molecular diagnostic opportunities upon the genes of collagen, elastin, FGFR, cartilaginous proteins, vitamin D receptor, lysosomal and peroxisomal enzymes.

Lethal osteochondrodysplasias are characterized by generalized involvement and early mortality related to respiratory failure. Milder osteochondrodysplasias may benefit from surgical bone enlongement and other corrective surgery and rehabilitation programs.

Achondroplasia is the most common cause of disharmonic short stature with short limbs (megalencephaly, frontal bossing, depressed nasal bridge, facial bone hypoplasia, prognatism, narrow thorax, rhizomelic short limb dwarfism, brachydactyly, trident hands and hypotonia), determined by AD Gly380Arg mutation in FGFR3 gene, with a high *de novo* mutation rate related with advanced paternal age. Thanatophoric dwarfism is a severe bone dysplasia (micromelic dwarfism with bowing of long bones, telephone receiver femurs, narrow thorax, severe platyspondily, facial bone hypoplasia and craniosynostosis) with high perinatal lethality, due to a *de novo* AD mutation in FGFR3 gene. Campomelic dwarfism is a severe bone dysplasia with high perinatal lethality and female prevalence, due to AR mutations in SOX9 gene. The phenotype includes sex reversal, macrocephaly, large fontanels, micrognathia, short neck, pectus carinatum, short limb dwarfism, talipes, anterior bowing of tibiae and poor ossification signs [18]. Diastrophic dysplasia is a rare condition due to AR mutations in SLC26A2 gene. Newborns show rhizomelic short limb dwarfism, bilateral clubbed foot, premature calcification of the costal cartilages, kyphoscoliosis, hip contractures, cleft palate and "hitchhiker" thumb due to deformity of the first metacarpal. Osteogenesis imperfecta is a genetically (type 1 collagen genes) and phenotypically (four different clinical variants) heterogeneous group of conditions characterized by frequent bone fractures [19]. Osteodysplastic primordial dwarfism is a brachymelic microcephalic dwarfism (prominent eyes, microretrognathia, high arched palate, oligodontia, sparse scalp hair, pectus carinatum, multiple skeletal abnormalities and sensory defects) with likely genetic heterogeneity and AR inheritance.

Genetic counseling and prenatal diagnosis

The improvement of knowledge and applications in biomedical sciences has contributed to the relevant advances in the prevention and early detection of genetic diseases. The most important tool for prevention is the genetic counseling, a nondirective communication/information process to the family in order to adopt conscious, responsible and coherent choices in dealing with genetic disease patients. Therefore, it is very important to achieve a confirmed diagnosis and up-to-date knowledge of natural history, prognostic and therapeutic implications, inheritance, recurrence risk and diagnostic opportunities (prenatal). Index case in the family as well as other risk factors (consanguinity, advanced maternal age, recurrent abortions, mutation carrier) require genetic counseling. Recurrence risk for multifactorial diseases may be given on the basis of empirical methods while in case of monogenic diseases (mendelian inheritance, genomic imprinting…) it can be estimated and communicated together with the available opportunities of genetic diagnosis.

Declaration of interest: The authors report no declarations of interest.

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