Congenital Malformations and Syndromes: Early Diagnosis and Prognosis in Neonatal Medicine

Giovanni Corsello and Mario Giuffrè

Contents

G. Corsello (✉) • M. Giuffrè
Department of Sciences for Health Promotion and Mother and Child Care, University of Palermo, Palermo, Italy
e-mail: Giocors@alice.it; mario.giuffre@unipa.it

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Abstract

Congenital malformations are defects of the morphogenesis of organs or body regions identified during intrauterine development or at birth. They may be isolated and single or multiple. Their global birth prevalence is about 2–3 %. Congenital defects may be caused by genetic and/or environmental factors, acting singly or in combination. A deep knowledge of the family and pregnancy histories, of the congenital anomalies and/or dysmorphic features' classification, as well as of the most appropriate cytogenetic and/or molecular genetic tests may facilitate the neonatologist to the newborn's correct assessment and management.

Salient Points

- Congenital malformations are defects of the morphogenesis that can be classified based on clinical, etiological, or pathogenetic criteria.
- The clinical and instrumental approach to congenital malformations and syndromes is a complex, long-lasting, and stressful process for both patients and their families.
- Diagnosis, treatment, and follow-up of congenital defects require the involvement of a multidisciplinary team of different specialists.
- Improvement in diagnostic and therapeutic resources has determined an increase in survival and quality of life for many conditions with congenital defects.
- Congenital malformations and syndromes are a major issue for health services in terms of costs and resources.

Introduction

The genetic counseling has been recently defined as a unique combination of intense science, critical thinking, and empathic process. This multidimensional definition contains all domains for a correct approach to a newborn with congenital malformations, but at the same time, it highlights several critical issues for the clinician who needs to start an early approach soon after birth or even prenatally. Modern diagnostic tools and therapeutic resources have allowed better identification of congenital malformations and have reduced long-term morbidity and mortality in affected patients. Because of increased life expectancy, congenital malformations today represent a major issue in health care because of the resources needed for multidisciplinary care.

Classifications

Based on clinical criteria, *major malformations* are defined as defects causing functional impairment and therefore needing medical or surgical treatment. Defects that do not produce functional impairment and do not require medical intervention are termed *minor malformations* if their prevalence at birth is less than 4 % and *phenotypic variants* when the birth prevalence is higher. Major and/or minor congenital malformations are frequently associated; apparently isolated defects may be associated with malformations that are not clinically evident at birth.

On the basis of etiological criteria, it is possible to distinguish primary malformations, secondary malformations (disruptions), and deformations (Table 1). *Primary malformations* are morphogenic defects arising from an intrinsic error of development with a genetic origin. *Disruptions* occur when an environmental factor interferes with an otherwise normal developmental process, causing global impairment or specific damage affecting a single developmental region. The causes of secondary malformations may be biological, chemical, metabolic, or physical. *Deformations* arise from extrinsic mechanical compression of one or more regions of the body during fetal development. The most common causes of deformations are amniotic bands, twinning, uterine malformations, and masses.

Patients with multiple malformations can be classified as having syndromes, sequences, associations, or dysplasias. *Syndromes* are conditions where all the structural defects arise from a single etiological factor, which may be genetic or

Table 1 Etiologic classification of congenital malformations

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

environmental. *Sequences* are characterized by a cascade of dysmorphic processes, linked by a cause/effect relationship with a single initiating event. Thus, a primary defect may induce several secondary defects, which are chronologically and pathogenetically related. *Associations* are sporadic events with different defects being present more frequently than would be expected if they were random events, without evidence of any etiological or pathogenetic relationship. In recent years, some associations have been recognized as disorders of blastogenesis, which are caused by genetic or environmental factors that interfere with early development when the embryo is a single developmental field, and producing defects in apparently unrelated organs and body regions. Blastogenesis is the first 4 weeks after conception and is characterized by processes that determine the midline and body axes, symmetry and lateralization, neurulation, and somite formation. Some associations are identified by an acronym of the defects, such as VACTERLS (vertebral defects, anorectal atresia, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, renal anomalies, limb defects, single umbilical artery) and MURCS (Mullerian duct aplasia, renal dysplasia, cervical somite anomalies). *Dysplasias* are structural defects involving specific tissues where a single gene mutation may determine the abolition or reduction of protein synthesis as well as the production of defective proteins.

Clinical Considerations

The birth of a baby with congenital malformations is the starting point of a clinical process that is aimed at making a precise diagnosis (Wiedemann et al. 1992; Twining et al. 2000). This leads to appropriate clinical planning and definition of prognosis and counseling of the parents. Different causal pathways may lead to a similar phenotype (Donnai and Winter 1995; Jones 1997), and the diagnostic process may be long and difficult, requiring follow-up to establish the natural history of the disorder. The diagnostic process includes an accurate history and description of the phenotype, with appropriate imaging and laboratory tests. Improvements in informatics have led to the development of computerized systems to improve diagnostic accuracy. The history should include

consideration of the whole family with the definition of a genealogical tree and the identification of risk factors (consanguinity, multiple abortions, stillbirths, advanced maternal and/or paternal age), the preconceptional period and environmental factors (infections, maternal metabolic diseases, diabetes mellitus, drugs, alcohol), and the pregnancy. Analysis of the phenotype is aimed at the identification and description (with photographic documentation) of structural defects (isolated and multiple, major and minor) and should include a description of clinical associations with genetic syndromes, such as developmental delay, growth restriction, disorders of sexual differentiation, or pubertal development.

Genetic Counseling and Prenatal Diagnosis

Genetic counseling has been recently defined as unique combination of intense science, critical thinking, and empathy counseling (Barry 2015). It consists in a nondirective process of communicating with and giving information to a family (usually the parents) to enable the making of decisions relating to patients with genetic diseases that are considered, responsible, and rational. It is important that genetic counselors have (a) a confirmed diagnosis for the index patient, (b) an up-to-date knowledge of the natural history of the disease, (c) an understanding of its prognostic and therapeutic implications, (d) knowledge of its pattern of inheritance, and (e) an awareness of the possibilities for early (prenatal) diagnosis. The main factors that determine a need for genetic counseling are the presence of an index case with a congenital malformation or of genetic disease in the family as well as the presence of parental risk factors (consanguinity, advanced maternal age, recurrent abortions, mutation carrier). If the disease is multifactorial (due to a combination of genetic and environmental factors), a recurrence risk may be given only on the basis of an empirical approach that takes account of the prevalence in a certain population or at a certain maternal age, number of affected subjects, and consanguinity within the family. In the case of monogenic diseases with Mendelian inheritance (autosomal dominant, autosomal recessive, X-linked), the relative recurrence risk must be explained to the family, who must also be informed about available opportunities for early diagnosis (preconceptional, prenatal, neonatal). The recent identification of complex genetic mechanisms (genomic imprinting, uniparental disomy, triplet amplification) has increased the number of diseases in which it is possible to give helpful genetic counseling.

Associations

Associations are usually sporadic conditions with a low recurrence risk. Environmental factors (alcohol, drugs, maternal diabetes) as well as chromosomal and single gene disorders may interfere with the blastogenic processes. A genetic background may also increase an individual's susceptibility to environmental factors.

VACTERLS Association

VACTERLS association is characterized by the manifestation of some or all of the defects summarized by the acronym: *v*ertebral defects, *a*norectal atresia, *c*ardiac anomalies, *t*racheoesophageal fistula, *e*sophageal atresia, *r*enal anomalies, *l*imb defects, *s*ingle umbilical artery. Tracheoesophageal and anorectal defects require early surgery during the neonatal period. The most frequent heart defects affect the ventricular septum. Limb defects include radial ray abnormalities (radial hypoplasia, thumb aplasia, or hypoplasia as well as its duplication), polydactyly, and syndactyly. Other features may be prenatal and postnatal growth restriction and ear and external genitalia abnormalities. VACTERLS association is often sporadic with a low recurrence risk. It is more frequent in the offspring of diabetic mothers. In some patients with associated obstructive hydrocephalus, gene mutations with autosomal recessive (AR) inheritance have been documented. Antenatal diagnosis can be challenging, as certain features can be difficult

to ascertain prior to birth. Management typically centers around surgical correction of the specific congenital anomalies (typically anal atresia, esophageal atresia, and certain types of cardiac malformations) in the immediate postnatal period, followed by long-term medical management of sequelae of the congenital malformations. If optimal surgical correction is achievable, the prognosis can be relatively good, though some patients will continue to be affected by their congenital malformations throughout life (Solomon 2011; Shaw-Smith 2006). Most patients have normal cognition, although they may present as failure to thrive and with neuromotor disabilities.

Infants of Diabetic Mothers

Congenital malformations in the offspring of diabetic mothers are clinically heterogeneous. Their frequency is two- to fourfold higher than in the general population. The relative risk for malformations is much higher in newborns of women with type 1 insulin-dependent diabetes mellitus and is inversely correlated with the effectiveness of maternal glycemic control, particularly during the periconceptional period. Several factors are involved in the pathogenesis of such defects: hyperglycemia, hyperglycosylation of proteins involved in differentiation, chronic hypoxia, polycythemia/hyperviscosity, and lactic acidosis (Mitanchez et al. 2015). All these factors may interact and interfere with blastogenesis, inducing abnormalities of the midline structures and symmetric organs. All types of malformations (skeletal, cardiac, renal, gastrointestinal, CNS) are more common in the infants of diabetic mothers. Some are specific, such as caudal dysgenesis, characterized by defects of vertebral, urogenital, and intestinal structures arising from the caudal mesoderm, with a wide spectrum of expression including sirenomelia, in which there is also a complex vascular defect. The fetus may be macrosomic because of fetal hyperinsulinemia, although a placental microangiopathy may also cause intrauterine growth restriction.

Table 2 Main malformation sequences

Name	Developmental field and organs involved
Holoprosencephaly	Precordial mesoderm, prosencephalic vesicle, rhinencephalon, orbits, nose, premaxilla
Septo-optic dysplasia	Optic chiasm, hypophysis
Pierre Robin	Jaw bone, oropharyngeal region
Poland	Pectoral muscle, superior limb
Klippel-Feil	Spine
Potter	Kidneys, urinary tract, lungs, limbs, facies
Prune belly	Urinary tract, abdominal wall
Bladder-cloacal exstrophy	Periumbilical mesoderm
Rokitansky	Muller ducts
Sirenomelia	Caudal mesoderm
Caudal regression	Caudal mesoderm
Premature rupture of amnion	Median axis, limb deformations, facial clefts
Fetal akinesia	Multiple body regions
Twin-twin disruption sequence	Multiple body regions

Sequences

Malformation sequences may be caused by genetic as well as environmental factors. Several organs and systems may be involved in malformation sequences (Table 2).

Holoprosencephalic Sequence

Holoprosencephalic sequence presents at birth with a wide spectrum of defects of the encephalon and the median craniofacial areas due to a developmental defect of the median subdivision of the prosencephalic vesicle and surrounding mesoderm.

Three anatomical variants (alobar, semilobar, and lobar) and four clinical variants (cyclopia, ethmocephaly, cebocephaly, and premaxillar agenesis) have been described. Clinical evaluation must include CNS imaging to define the full phenotype. The severity of CNS defects is the main reason for the high and early lethality of the condition. If the phenotype is only partially

expressed, longer survival is possible, frequently associated with relevant neurologic problems. The parents and relatives of patients must be investigated for minor signs of the sequence (hypotelorism, single median incisor) in order to recognize a possible autosomal dominant (AD) inheritance (Dubourg et al. 2011; Lami et al. 2013).

The etiology is very heterogeneous: from chromosomal abnormalities (such as trisomy 13), known syndromes (such as Smith-Lemli-Opitz syndrome, CHARGE syndrome) to environmental factors (maternal diabetes or hypocholesterolemia during gestation). In nonchromosomal non-syndromic holoprosencephalic sequence, at least 14 genes have been implicated: four major genes *SHH*, *ZIC2*, *SIX3*, and *TGIF* and ten minor genes. Molecular analyses of the four main genes are routinely performed with a mutation detection rate of 25 %. Array-CGH (comparative genomic hybridization) analysis shows 22 % microrearrangements in HPE (Winter et al. 2015). However, the underlying genetic complexity is to be clarified yet; most cases are supposed to be multifactorial and the recurrence risk for families with a sporadic case is estimated at around 6 %.

Pierre Robin Sequence

Pierre Robin sequence is a developmental defect of the mandible and surrounding oropharyngeal region. It is characterized by microretrognathia, cleft palate, and functional disturbances (swallowing deficit, respiratory distress). A deficiency of mesoderm induction may cause a primary cleft palate (V-shape). Alternatively, the cleft palate may be secondary to jaw arch hypoplasia, which leads to the position of the tongue being fixed between the palatine processes, causing a defect of fusion of the secondary palate in the midline (U-shape). Respiratory obstruction is caused by the tongue falling backwards and by a primitive pharyngeal stenosis (secondary to a migration deficit of neural crest cells). The sequence may present with a wide phenotypical spectrum, either in isolation or as part of a more complex syndrome (del 18q, Stickler syndrome, del 22q11, etc.). All these variables influence the prognosis (Thouvenin et al. 2013). Newborns may require prolonged respiratory and/or nutritional support and long-term hospitalization and follow-up. In the most severely affected cases, surgery to the jaw distraction may improve the outcome.

Potter Sequence

The Potter sequence is caused by absent or severely reduced fetal urine output from the first trimester. It may be secondary to bilateral renal agenesis (a differentiation defect of the metanephric blastema) or to other renal and urinary tract malformations. The cascade mechanism starts with diminished urine production by the fetus; this leads to a reduced volume of amniotic fluid (anhydramnios or oligohydramnios), which gives rise to pulmonary hypoplasia, leading to respiratory distress at birth, facial dysmorphism (prominent nose and flat profile), and diminished fetal movements with multiple postural deformations particularly of the lower limbs. When the phenotype is fully expressed, the severe renal and pulmonary damage is responsible for the high perinatal mortality (Shastry et al. 2012). Prenatal diagnosis by ultrasound reveals the kidney defect, oligohydramnios, and other associated malformations. The sequence is often sporadic, with etiological heterogeneity and a recurrence risk of about 3 %. It may occasionally be associated with other defects in a more complex syndrome (Meckel-Gruber syndrome: occipital encephalocele, renal cystic disease, polydactyly, and an autosomal recessive inheritance).

Prune Belly Sequence

This sequence was named because of the characteristic appearance of the abdomen (wrinkled skin, also referred to as “flabby abdomen”) in the affected newborns. The sequence may be related to various defects of the genitourinary tract, involving the proximal urethra (urethral agenesis,

cloacal persistence, urethral stenosis, posterior urethral valves in males) (Smolkin et al. 2008). Urethral obstruction is responsible for oligohydramnios (and possible secondary Potter sequence) and accumulation of urine in the proximal renal tract, leading to parenchymal damage (bladder dilatation, bilateral ureteric dilatation, and hydronephrosis). Bladder hypertrophy and dilatation may interfere with development of the abdominal wall muscles and diaphragm and testicular migration in the scrotum in males (cryptorchidism). Abdominal wall muscle hypoplasia is responsible for the prune belly appearance because of visible intestinal loops through the thin abdominal wall. Diaphragmatic defects and oligohydramnios cause lung hypoplasia and severe respiratory distress at birth. Although early prenatal diagnosis by ultrasonography is possible, the differential diagnosis between isolated renal cystic conditions and obstructive uropathies may be difficult. Prenatal bladder catheterization allows urine to flow into the amniotic cavity and must be followed by surgical correction after birth.

Syndromes

Chromosomal Abnormalities

The overall incidence of chromosomal anomalies is estimated at about 1:170 live births. Their prevalence at conception is much higher, giving rise to a spontaneous abortion or fetal death because of developmental impairment. About 50 % of spontaneous abortions have an abnormal chromosomal structure. Chromosomal aberrations may affect *autosomes* and/or *sex chromosomes* and may involve their number or structure. *Numeric aberrations* have a prezygotic origin (meiotic nondisjunction, frequently related to advanced maternal age). They may also arise from a postzygotic error when they are present only in a variable proportion of cells (mosaics). *Structural aberrations* may occur de novo from a meiotic rearrangement or may be inherited from one parent, who carries a balanced non-symptomatic chromosomal translocation.

Down Syndrome (Trisomy 21)

Down syndrome is the most frequent chromosomal aberration at birth (about 1:700). It is determined by a trisomy of chromosome 21. In most (95 %) cases, trisomy 21 is secondary to a maternal meiotic nondisjunction of homologous chromosomes 21; more rarely there may be a Robertsonian translocation or a postzygotic mitotic nondisjunction (mosaic with milder phenotype). The incidence is related to maternal age at conception (1/1,500 at 20 years and 1/28 at 45 years). The overall recurrence risk is low (about 1 %), although it significantly increases when one of the parents carries a balanced translocation. The phenotype at birth is characteristic: main facial features are Brushfield spots (gray spots in the median zone of the iris), upslanting palpebral fissures, epicanthal folds, small nose, small mouth with prominent tongue, flat facial profile, brachycephaly with a flat occipital bone, small low-set ears, and short neck with redundant skin folds. Newborn babies are hypotonic with lax joints. A single palmar crease and clinodactyly of the little finger are frequent. Organ involvement includes congenital heart defects (atrioventricular canal, ventricular septal defects, tetralogy of Fallot), duodenal atresia or stenosis, Hirschsprung's disease, hypothyroidism, and urinary tract malformations. Long-term follow-up is required because of developmental delay, intellectual disability, growth retardation, occurrence of autoimmune diseases, immunodeficiencies, and leukemia (Karmiloff-Smith et al. 2016). Survival rates and the quality of life have improved significantly with educational and screening programs and the development of multidisciplinary follow-up.

Edwards Syndrome (Trisomy 18)

Edwards syndrome is determined by trisomy of chromosome 18, sometimes as a mosaic or in association with other chromosomal abnormalities. Its birth prevalence is about 1:8,000 because most affected fetuses abort spontaneously. Newborns show severe prenatal growth restriction, dolichocephaly with prominent occiput and low-set dysplastic external ears, jaw hypoplasia, flexed hands with the index finger overlapping the

middle finger, single palmar crease, and talipes with rocker-bottom feet. There are frequently associated malformations (heart, renal, intestinal, CNS), which are responsible for the very grave prognosis and high neonatal mortality (Wu et al. 2013).

Patau Syndrome (Trisomy 13)

Patau syndrome is determined by trisomy of chromosome 13, sometimes with chromosomal translocation or rarely as mosaic. Its birth prevalence is about 1/10,000. Newborns show prenatal growth restriction, a small trigonocephalic skull, areas of aplasia cutis on the scalp, cleft lip and palate, microphthalmia, variable hypotelorism up to cyclopia (i.e., expression of an associated holoprosencephalic sequence), postaxial polydactyly and/or syndactyly, forced flexion of the fingers, single palmar crease, plantar convexity, and cryptorchidism. Other organs are frequently involved (heart, kidneys). Patients with fully expressed phenotype usually die during the first month of life; those with milder signs (mosaics) may survive with severe developmental deficits (Wu et al. 2013; Barry et al. 2015).

Wolf-Hirschhorn Syndrome (4p-)

This is a rare condition determined by deletion of the distal part of the short arm of chromosome 4. Newborns present with prenatal growth restriction, hypotonia, severe microcephaly with brachycephaly, prominent nose, downturned corners of the mouth, arched palate, jaw hypoplasia, hypertelorism, downslanting palpebral fissures, iris coloboma, and large low-set external ears. Heart, renal, and skeletal defects are frequent. The degree of extension of the chromosomal deletion influences the severity of phenotype and neonatal mortality rate. Surviving patients show severe postnatal growth retardation and psychomotor developmental delay.

Cri du chat Syndrome (5p-)

Cri du chat syndrome is due to a variable deletion of the short arm of chromosome 5, named because of the characteristic high-pitched catlike cry of affected newborns caused by hypoplasia of laryngeal cartilages, which disappears after the first months of life (Rodríguez-Caballero et al. 2012). Other phenotypical features are microcephaly, round face, hypertelorism, micrognathia, epicanthal folds, and low-set ears. At birth there is generalized hypotonia. Later there is limb hypertonia and severe developmental delay.

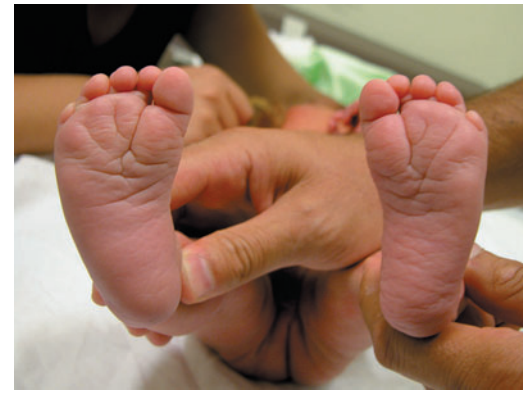

Fig. 1 Deep plantar grooves in a newborn with mosaic 8 chromosome trisomy

Mosaic 8 Chromosome Trisomy

The full trisomy of chromosome 8 is extremely rare in humans. It is more common as a mosaic. The phenotype of mosaic trisomy 8 includes scaphocephaly, ankylosed large joints, clubfoot, absent or hypoplastic patellae, arachnodactyly, and brachydactyly. Deep grooves in the palms and soles (Fig. 1) are virtually diagnostic in infancy but become less prominent with age (Biesecker and Spinner 2013). The face is characterized by a prominent pouting lower lip and small jaw. Intellectual disability may be present but is often mild and may remain undetected.

Turner Syndrome

Turner syndrome is the most frequent aneuploidy of sex chromosomes with a birth prevalence of 1/2,500. It is determined by a monosomy of chromosome X, which may be complete (50 %) or partial (20 %); it frequently presents as a mosaic with a milder phenotype (30 %). During the neonatal period, the diagnosis is suspected because of lymphedema of the hands and feet (Fig. 2), nail dysplasia, neck pterygium, a large mouth with downturned corners, dysplastic

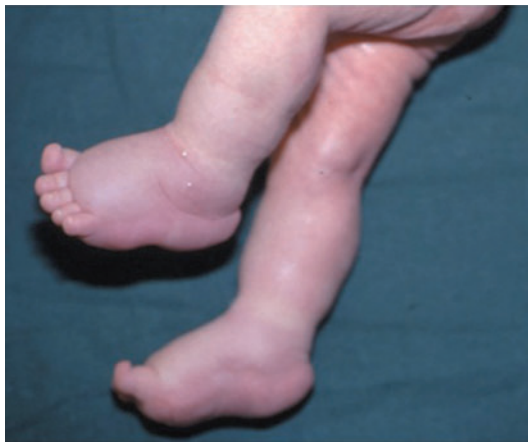

Fig. 2 Foot lymphedema in a baby with Turner syndrome

external ears, and left heart output defects (aortic coarctation, left heart hypoplasia). In addition, there may be a prenatal history of cystic hygroma. The clinical phenotype changes with age when other features become evident: short stature, short neck, low posterior hairline, restricted thorax, cubitus valgus, shortness of the fourth metacarpal bone, primary amenorrhea, absence of secondary sexual signs, and an endocrine profile of gonadal dysgenesis. Life expectancy is not reduced, but long-term follow-up is required and appropriate hormonal therapy (growth hormone in the first decade and estrogen-progesterone after puberty must be given in order to improve height and induce the menstrual cycle) (Blum et al. 2013).

DiGeorge Syndrome

DiGeorge syndrome, also noted as 22q11.2 deletion syndrome, is a chromosomal disorder whose common features include cardiac defects, palatal anomalies, facial dysmorphism, developmental delay, and immune deficiency (McDonald-McGinn and Sullivan 2011; Botto et al. 2003). This condition has been previously reported with the acronym CATCH 22 (Cardiac abnormality, Abnormal face, Thymic hypoplasia, Cleft palate, Hypoparathyroidism, chromosome 22 microdeletion).

Heart defects are conotruncal (aortic arch interruption, common arterial trunk, tetralogy of Fallot). When the brachial structures are involved, there is dysfunction of the immune system (T-cell deficiency) and parathyroidal abnormalities with low serum calcium levels. During the neonatal period, the full expression of the phenotype results in hypocalcemia and craniofacial dysmorphism (micrognathia, cleft palate, anteverted nares, low-set external ears) with a conotruncal heart defect and absent thymic shadow at chest X-ray delineating the phenotype with full expressivity. In most cases, the syndrome is due to a 3 Mb deletion on the chromosomal region 22q11.2; there are also atypical deletions which are nested within the DiGeorge critical region. Some of them include the *TBX1* gene that has been shown to be implicated in cardiac, parathyroid, thymus, and facial structure development. The variable expression of the 22q11.2 phenotype is thought to be due to genetic modifiers on either the other 22q11.2 allele or on other chromosomes. Diagnosis is suspected upon clinical examination and detection of anomalies but needs to be confirmed by detection of the 22q11.2 deletion, using fluorescence in situ hybridization (FISH), MLPA, aCGH, or genome-wide SNP (single nucleotide polymorphism) microarrays (Hacıhamdioğlu et al. 2015).

Monogenic Disorders

Monogenic disorders are single gene mutations with a Mendelian mode of inheritance. The genotype-phenotype correlation remains undefined 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) in the same family and appears to depend on interference by other genetic and/or environmental factors. In addition, epigenetic factors (e.g., DNA methylation) may act during the differentiation processes to modify gene expression and may depend on the parental origin of the gene (genomic imprinting).

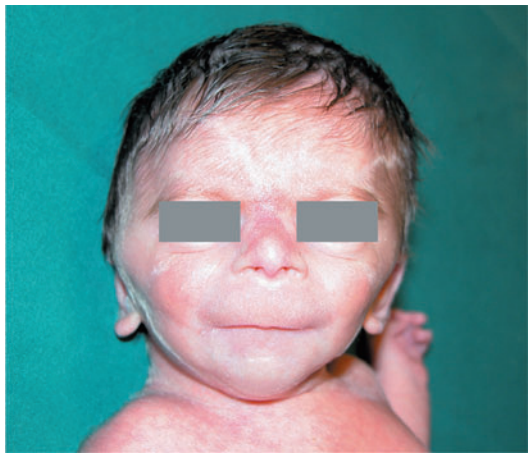

Fig. 3 Typical facial appearance of a newborn baby with Cornelia de Lange syndrome, showing synophrys, a depressed nasal bridge, anteverted nares, long philtrum, and carp mouth

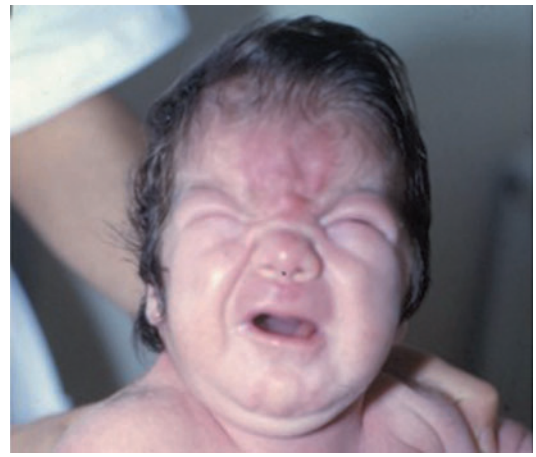

Fig. 4 Newborn with Rubinstein-Taybi syndrome showing microcephaly, frontal bossing, downslanting palpebral fissures, broad nasal bridge, beaked nose, epicanthus, and maxillary hypoplasia

Cornelia de Lange Syndrome (CdLS)

CdLS affects 1/10,000 newborns and is usually sporadic. Causative mutations in genes involved in chromosomal cohesion (cohesin complex) have been identified. The *NIPBL* gene (locus at 5p13.1) is mutated in approximately 50 % of patients and is the major gene involved in the syndrome. Mutations in *SMC3*, *RAD21*, *SMC1A*, and *HDAC8* have recently been described with an autosomal dominant or an X-linked dominant pathways of inheritance. Newborns show a typical facial appearance (microbrachycephaly, low anterior and posterior hairline, synophrys, small nose with a depressed nasal bridge, anteverted nares, long philtrum, "carp" mouth, maxillary prognathism, low-set ears, Fig. 3), with intrauterine and postnatal growth retardation, hypertrichosis, and upper limb anomalies (small limbs, reduction defects including phocomelia, limited elbow extension, single palmar crease, oligosyndactyly) (Bhuiyan et al. 2006; Ramos et al. 2015).

Urogenital, heart, and intestinal malformations may also be present. Most patients show developmental delay and growth retardation. Infections, feeding difficulties, and neurologic disturbances (seizures, motor and speech retardation) require long-term multidisciplinary follow-up and family support.

Rubinstein-Taybi Syndrome (RSTS)

RSTS is a rare malformation syndrome characterized by intellectual disability, facial abnormalities, and broad thumbs and toes. Chromosome abnormalities are occasionally observed on routine cytogenetic testing. *CREBBP* and *EP300* are the only genes currently known to be associated with RSTS. FISH analysis of *CREBBP* detects microdeletions in approximately 10 % of individuals with RSTS. Sequence analysis detects *CREBBP* pathogenic variants in another 40–50 % of affected individuals. Pathogenic variants in *EP300* are identified in approximately 3–8 % of individuals with RSTS (Schorry et al. 2008; Pagon et al. 1993). Familial cases with autosomal dominant inheritance have been described.

The diagnosis of RSTS is primarily based on clinical features. The main craniofacial features (Fig. 4) are microcephaly, frontal bossing, large anterior fontanelle, downslanting palpebral fissures, broad nasal bridge, beaked nose, epicanthal folds, strabismus, maxillary hypoplasia, high-arched palate, and external ear abnormalities. There is hand and foot involvement (broad distal phalanges of thumbs and halluces with medial deviation, clinodactyly, or duplication). There may also be hirsutism and abnormalities of the

skeleton (spinal, pelvic), heart (septal defects, patent ductus arteriosus), and urogenital tract (hypospadias, cryptorchidism). Growth retardation, skeletal maturation delay, and severe intellectual disability are more common with increasing age (Pagon et al. 1993).

Marfan Syndrome (MS)

MS is characterized by several congenital defect of the connective tissue involving the skeleton, eye, and cardiovascular system. It is determined by heterozygous mutations in the *FBN1* gene (15q21.1) encoding for fibrillin-1 protein, which is a component of collagen (Tiecke et al. 2001). Frontier forms have been identified, secondary to mutations in the *TGFBR2* gene located on chromosome 3 which encodes for a TGF-beta receptor. It is inherited as an autosomal dominant with variable clinical expression; about 25 % of cases are sporadic, due to de novo mutations correlated with advanced paternal age. Newborns show arachnodactyly, long and thin limbs, increased length joint laxity and hypermobility, muscular hypotonia, hernias, and pectus carinatum or excavatum. Cardiac abnormalities comprise mitral valve prolapse and aortic defects (aortic root dilatation and aortic aneurysm). Patients with most severe neonatal phenotype (neonatal Marfan syndrome) have high early mortality rates. Skeletal and cardiac problems usually evolve with growth (kyphoscoliosis, progressive aortic dilatation, aortic dissection) and ocular signs develop (ectopia lentis, early glaucoma) (Loeys et al. 2010).

Noonan Syndrome (NS)

NS is a relatively frequent (1/2,000) condition with some phenotypic features similar to those of Turner syndrome (male Turner, pseudo-Turner). In approximately 50 % of cases, the disease is caused by missense mutations in the *PTPN11* gene (12q24.1), resulting in a gain of function of the non-receptor protein tyrosine phosphatase SHP-2 protein. Recently, mutations in other genes from the RAS-MAPK pathway (*KRAS*, *SOS1*, and *RAF1*) have been identified in a small portion of patients with NS. Mutation analysis can be carried out on blood samples and should be recommended for any subject with a suspected diagnosis of NS. However, the diagnosis cannot be excluded on a molecular basis, as the sensitivity of combined screening of all known genes allows confirmation in less than 75 % of patients, with sporadic as well as familial cases (Roberts et al. 2013). The inheritance is autosomal dominant and parents must be always investigated for mild clinical signs.

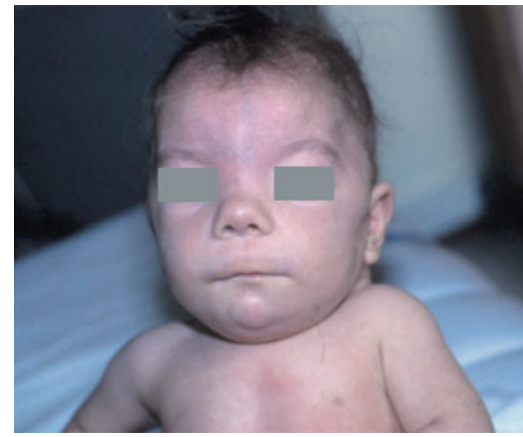

Fig. 5 A patient with Noonan syndrome with hypertelorism, upslanting palpebral fissures, and shield chest

Newborns show hypertelorism, upslanting palpebral fissures, low-set posteriorly rotated ears, neck pterygium, a shield chest with deformation of the sternum, and lymphedema (Fig. 5). Cardiac involvement is mainly of the pulmonary outflow tract (pulmonary valve dysplasia and stenosis, cuspid thickening, and hypomobility). Other possible features are cryptorchidism in males and a bleeding tendency, due to thrombocytopenia and partial deficiency of coagulation factors. Later in infancy, other signs become evident: postnatal growth retardation (with short stature and retarded bone age), triangular face, mild psychomotor, and intellectual delay (Ferrero et al. 2008). The differential diagnosis should include Turner syndrome, cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis type 1, and LEOPARD syndrome. Life expectancy depends exclusively on the severity of heart defects.

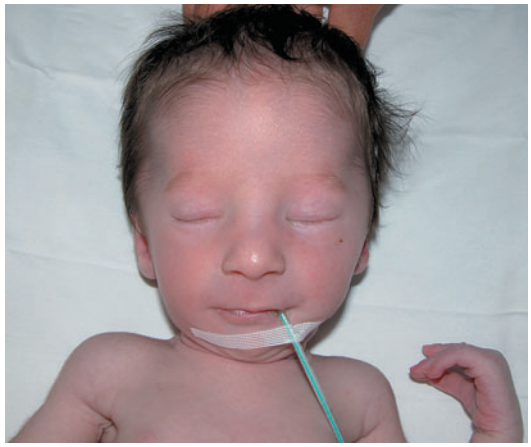

Fig. 6 The neonatal phenotype of Prader-Willi syndrome: hypomimic face, reduced bitemporal diameter, almond-shaped eyes, small mouth with downturned corners, and thin upper lip

Prader-Willi Syndrome (PWS)

Prader-Willi syndrome is determined by the failure of expression of genes of paternal origin in the 15q11-q13 region. These genes are normally subjected to maternal imprinting (DNA methylation) which avoids maternal copy transcription and determines a functional gene monosomy (only the paternal copy is expressed). This condition may arise from microdeletions of paternal chromosome 15 (70–75 %), maternal uniparental disomy (25–30 %), or imprinting center defects (1 %). Methylation testing identifies almost all patients; FISH and microsatellite DNA analysis may reveal microdeletions and maternal UPD. PWS newborns (Fig. 6) present with congenital hypotonia, a prenatal history of reduced fetal movements, poverty of facial expression, dolichocephaly with reduced bitemporal diameter, almond-shaped eyes with upslanting palpebral fissures, a small mouth with downturned corners and thin upper lip, small hands and feet, and genital hypoplasia with cryptorchidism in males (Gunay-Aygun et al. 2001). Hypotonia of the respiratory, orofacial, and pharyngoesophageal muscles causes variable degrees of respiratory and feeding difficulties (poor suction and swallowing), which are present from birth and tend to improve after the neonatal period. After the first year of life, the phenotype modifies and is characterized by hyperphagia, obesity, sleep disturbances, short stature, hypogonadotropic hypogonadism, mild to moderate mental retardation, and speech delay. Treatment with growth hormone (GH) is possible and good clinical results have been reported (Wolfgram et al. 2013).

Beckwith-Wiedemann Syndrome (BWS)

Beckwith-Wiedemann syndrome is a sporadic condition determined by an altered balance between cooperating genes in the region 11p15. The genetic mechanism is complex and involves imprinted genes encoding for several important growth factors and receptors. Various genotypic abnormalities have been described in BWS patients, e.g., microduplication of paternal region 11p15, microdeletion of the maternal region, and mutations and paternal uniparental disomy of chromosome 11. Molecular subgroups are associated with different recurrence risks and different clinical findings (e.g., tumor risks) (Weksberg et al. 2010).

The main neonatal clinical features (Fig. 7) are exomphalos, macroglossia, and gigantism (EMG syndrome). Other features are visceromegaly, adrenocortical cytomegaly, dysplasia of the renal medulla, typical linear indentations of the helix and the auricular lobe of the ear, hypoglycemia during the first days of life, and limb hemihypertrophy. Prenatal diagnosis may be because of exomphalos and generalized overgrowth seen on ultrasound scanning. The neonatal diagnosis is based on clinical findings, although careful molecular cytogenetic analysis of the 11p15 region is recommended. Overgrowth and macroglossia tend to become less evident with age, but there is an increased risk of malignant tumors (Wilms' tumor, adrenal carcinoma, hepatoblastoma).

Silver-Russell Syndrome

Silver-Russell syndrome is a sporadic condition with genetic heterogeneity. Most cases are sporadic. Maternal uniparental disomy of chromosome 7 is observed in 10 % of patients. Approximately 30 % of the cases show hypomethylation of the *H19* gene, located in

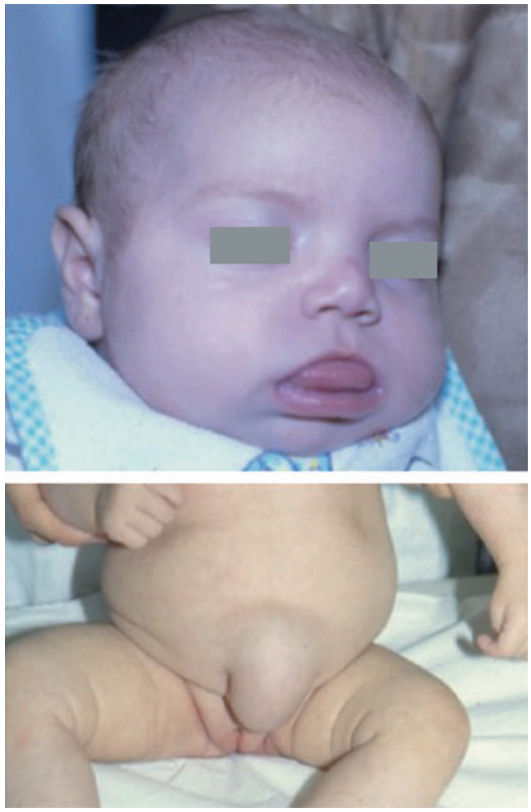

Fig. 7 Exomphalos, macroglossia, and gigantism

the 11p15 imprinted region. Hypomethylation results in most cases from an epigenetic mechanism or a genomic micro-rearrangement, such as a maternal microduplication of the region. Diagnosis is mainly clinical, as there is no specific biological test, but it can be confirmed by the detection of the underlying molecular anomaly with methylation-specific PCR, microsatellite typing, methylation-specific MLPA, and/or array CGH (Abu-Amero et al. 2008; Eggermann et al. 2011). The neonatal phenotype is characterized by severe intrauterine growth restriction with normal development of the skull (pseudohydrocephalic appearance), poor postnatal growth, craniofacial features (triangular-shaped face and broad forehead), body asymmetry, and a variety of minor malformations (clinodactyly and syndactyly of the little finger). The phenotypic expression changes during childhood and adolescence, with the facial features

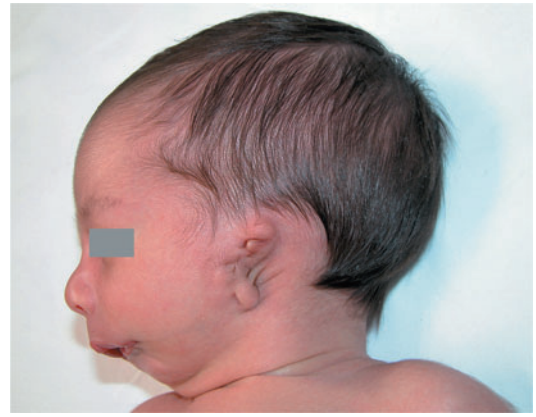

Fig. 8 Hemifacial microsomia and atresia of the external auricle in a baby with Goldenhar syndrome

and asymmetry usually becoming more subtle with age. GH therapy should be considered to improve final height.

Goldenhar Syndrome (GS)

GS is a spectrum of malformations involving the eye, ear, and vertebrae with heterogeneous etiology and a highly variable phenotype (Gorlin et al. 1990). Its prevalence at birth is about 1/5,000. Most cases are sporadic, although some families with autosomal dominant inheritance have been described. GS originates from a vascular disruption of the first and second branchial arches, with consequent malformations of related organs and tissues. Defects are more often unilateral and an increased incidence has been reported in the offspring of diabetic mothers, as have other disorders of blastogenesis. GS newborns show multiple craniofacial anomalies (Fig. 8): hemifacial microsomia, ipsilateral deformity of the external ear (preauricular tags, atresia of the external auditory canal, anomalies in size and shape of the external auricle), epibulbar dermoid, and coloboma of the upper eyelid. In addition, defects of the cervical vertebrae (hemivertebrae, fusions, segmental agenesis), cleft palate, choanal atresia, heart, kidney, and CNS defects may be found. Auditory function must be assessed early to preserve speech and cognitive development (Paludetti et al. 2012).

Smith-Lemli-Opitz Syndrome (SLOS)

SLOS is a rare (1/30,000) autosomal recessive condition, caused by mutations in the *DHCR7* gene (11q13.4) leading to deficiency of the enzyme 3 beta-hydroxysterol-delta 7-reductase that converts 7-dehydrocholesterol (7DHC) to cholesterol (Wassif et al. 1998; Porter 2008). The enzyme deficiency causes a severe deficit of endogenous cholesterol production and its derivative compounds (sexual steroids, components of the myelin and cellular membranes), starting from intrauterine life. SLOS newborns show intrauterine growth restriction, severe hypotonia, microdolichocephaly, high forehead, palpebral ptosis, anteverted nares, and micrognathia. There may be other features, such as agenesis of the corpus callosum, cleft palate, syndactyly of the second and third toes, congenital heart defects, and liver dysfunction. Male patients usually have hypospadias, micropenis, cryptorchidism, and sometimes various degrees of ambiguous genitalia, because of the prenatal androgen deficiency. Diagnosis is based on the detection of low cholesterol and elevated 7DHC levels in plasma or tissues and confirmed due *DHCR7* sequence analysis, which allows confirmation of the prenatal diagnosis for at-risk couples. Failure to thrive worsens with age and there is always severe psychomotor delay. Management is symptomatic and most patients are treated with dietary cholesterol supplementation. Treatment trials are underway investigating combined treatment with cholesterol supplementation and a HMG-CoA reductase inhibitor. Surgery is proposed in case of secondary problems due to malformations (Porter 2008).

Disruptions

Some congenital malformations can be related to exogenous factors, which act during intrauterine life, inducing abnormalities of developmental and differentiation processes. The most susceptible period is the first trimester of pregnancy in which the identification of developmental fields, organogenesis, and differentiation take place. Biological, chemical, metabolic, physical and mechanical agents (Table 1) may cause defects of morphogenesis. The etiologic identification is important for effective genetic counseling and reducing the risk of recurrence in an affected family.

Biologic Agents

Most morphogenetic defects determined by biological agents are pathogenetically and clinically characterized. A high IgM level soon after birth is strongly suggestive of a prenatal infection of the fetus, although only 30 % of these newborns show clinical consequences. The earlier the timing of intrauterine infection (particularly during the first trimester of gestation), the more severe is the effect of morphogenetic defects due to viral and bacterial agents, and there is usually associated intrauterine growth restriction. The most common embryofetopathies due to biologic agents are described in Table 3.

Chemical Agents

Any substance introduced to the human organism can be considered as a chemical agent. They may be drugs or foods associated with flawed lifestyle choices (alcohol consumption, cigarette smoking, ingestion of substances of abuse) or produced by maternal metabolism in specific situations. Some drugs and single molecules, which are well tolerated by an adult, may be seriously dangerous for the development of the embryo and fetus. Drug testing in human pregnancy is difficult and all drugs have therefore to be considered potentially harmful, requiring careful risk/benefit evaluation. Substances may cross the placenta and reach the fetus and placental function may reduce or increase their effects. Individual metabolism may influence the clinical effects, dosage, and timing of administration. The most frequent disruptions by chemical agents are reported in Table 4.

Table 3 Main disruptions determined by biologic agents

Biologic agent	Phenotype
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, myocarditis, chorioretinitis, muco-hematic rhinitis, skeletal alterations (lacunae, caput quadratum, metaphyseal ossification defects, osteochondritis, and secondary pseudoparalysis)
Toxoplasma gondii	Hydrops, hydrocephalus, intracranial calcifications, chorioretinitis, cataract, seizures, hepatosplenomegaly, skin rush

Vascular Disruptions

Any vascular accident during early embryonic and fetal development may determine subsequent morphogenetic defects in the relevant body region.

Disruption of the subclavian artery includes a heterogeneous group of clinically and etiologically different conditions, characterized by alteration of different mesodermal structures supplied by the subclavian artery. Thus, the Poland sequence includes pectoral muscle agenesis and ipsilateral superior limb reduction defects. Kidney and urinary tract defects are frequently associated, expanding the phenotype toward an acropectoral-renal developmental field.

Twin-twin disruption sequence (TTDS) may involve various structures such as the brain, brachial arches, limbs, gut, and kidneys. It is caused by the intrauterine developmental impairment and

Table 4 Main disruptions determined by chemical agents

Chemical agent	Phenotype
Anticonvulsant drugs	Cleft lip and palate, neural tube defects, congenital heart defects
	Hydantoin (microcephaly, mental retardation, CNS abnormalities, small nose, facial bone hypoplasia, epicanthus, hypertelorism, strabismus, cleft lip and palate, micrognathia, short neck, heart defects)
	Trimethadione (microcephaly, facial bone hypoplasia, palpebral synophrys, epicanthus, 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, hypoplastic 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, hypocalcemia, ventricular septal hypertrophy, caudal dysgenesis, any kind of congenital malformations (skeletal, cardiac, renal, intestinal, CNS, etc.)
Maternal	Defects of cellular proliferation and migration with myelinization delay (IUGR, severe microcephaly, hypotelorism)
Hyperphenylalaninemia	Prominent nose, low-set dysplastic external ears, mental retardation, cleft lip and palate, conotruncal heart defects

subsequent death of a monozygotic twin. The presence of vascular placental anastomoses between the arterial supplies of twins and abnormal communicating flow allows the passage of thromboemboli to the surviving twin, with reduced or interrupted blood flow causing structural damage. The complex vascular interactions between monozygotic twins may result in other vascular disruptions (e.g., because of an acardiac twin) or a twin-twin transfusion sequence, which are particular features of monozygotic twins (Giuffrè et al. 2012).

Dysostoses

A heterogeneous group of birth defects with single or multiple involvement of skeletal segments (with no systemic cartilaginous tissue involvement), due to mutations of the genes involved in bone development. Dysostoses classification is based on phenotypic criteria and the body region most involved. In some instances, a genetic classification is now possible. Most syndromal craniosynostoses are determined by mutations in fibroblast growth factor receptor (*FGFR*) genes, with string evidence of genetic heterogeneity (the same condition being determined by different mutations in the same gene or in different *FGFR* genes) and genetic pleiotropism (the same mutation being responsible for different phenotypes). Genotype/phenotype correlation is not possible for all cases, and it can be influenced by other genes (epistatic) as well as other interactive cytoplasmic and environmental factors.

Craniofacial Dysostoses

Full fusion of all cranial sutures is normally achieved at about 25 years of age. Craniosynostoses depend on a precocious closure of one or more cranial sutures and may cause a restriction in the size of the cranium. The closure of a suture limits cranial growth at that site, and there is increased cranial growth at the other sutures, producing deformation of the skull (sometimes with brain growth restriction, hydrocephalus, and intracranial hypertension). Skull morphology depends on suture involvement (nature, timing, extension, and symmetry). The overall incidence of craniosynostoses is estimated to affect about 1/3,000 newborns. It may present in isolation or as part of a more complex syndrome.

Non-syndromal Craniosynostoses

Scaphocephaly depends on the premature fusion of the sagittal suture with consequent restriction of growth along the transverse axis and compensatory increased growth along the anteroposterior axis. *Plagiocephaly* depends on the premature fusion of a single coronal suture with consequent ipsilateral growth restriction and flattening of the frontal bone; the involvement of facial structures varies from simple deviation of nasal septum to severe asymmetry of the sphenoid and maxillary bones. *Brachycephaly* is due to premature fusion of both coronal sutures with consequent growth restriction along the anteroposterior axis and compensatory increase in skull height; hypoplasia of the frontal region is often present. Acrocephaly depends on the premature fusion of the coronal and sagittal sutures with consequent severe growth restriction along both anteroposterior and transverse axes and compensatory increased development of the frontal region. Intracranial hypertension is frequently present and requires early surgical correction to avoid severe CNS complications. *Trigonocephaly* is due to the premature fusion of the metopic suture, often evident because of a longitudinal bone crest in the median frontal region, giving the skull a triangular appearance with hypotelorism and flattening of the lateral frontal regions. *Cloverleaf skull* is due to the premature fusion of the coronal, sagittal, and lambdoidal sutures with excessive skull growth in height and to both sides, giving a trilobar appearance. Intracranial hypertension is consistently severe and gives rise to CNS complications.

Syndromal Craniosynostoses

Apert syndrome is a rare and serious phenotype described in newborns with acrocephaly and syndactyly of the hands and feet (Fig. 9). The premature fusion of both coronal sutures is responsible for acrocephaly, frontal bossing, flat

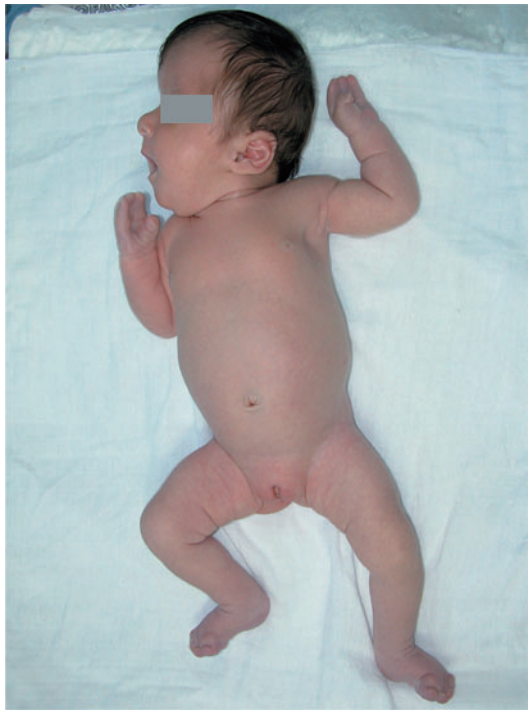

Fig. 9 Baby with Apert syndrome showing acrocephaly, frontal bossing, exophthalmus, small upturned nose, maxillary hypoplasia, and spoon-shaped hands

occipital bone, and facial dysmorphic features (downslanting palpebral fissures, exophthalmus, hypertelorism, small upturned nose, maxillary hypoplasia, low-set ears). Hands and feet present a complete syndactyly (spoon-shaped hand) with bone and nail fusion. Synostosis may also be found in the carpal and tarsal bones and cervical vertebrae. Mental retardation may be present, as well as intracranial hypertension, particularly in the absence of early neurosurgical correction. A complex surgical program must be planned for the correction of multiple synostosis (skull remodeling, hand surgery). Apert syndrome is due to mutations in the exon 7 of the *FGFR2* gene (different mutations have been identified), with autosomal dominant inheritance and a high rate of de novo mutations correlated with advanced paternal age (Wilkie et al. 1995).

Crouzon syndrome is the most frequently reported syndromal craniosynostosis, characterized by acrocephaly with no hand and foot involvement. Premature fusion of the coronal sutures causes the acrocephaly, frontal bossing, and flat occipital bone. Looking at the face, there is hypoplasia of the midline structures, reduced orbital volume and ocular proptosis, strabismus, a small upturned nose, and maxillary hypoplasia. Fusions of cervical vertebrae and mild mental retardation may occur. Crouzon syndrome may be due to different mutations of the *FGFR2* gene with a wide range of phenotypical expression. It may be sporadic, due to a de novo mutation often related to advanced paternal age or familiar with autosomal dominant inheritance.

Muenke syndrome is a relatively frequent unilateral coronal craniosynostosis with brachydactyly. It is caused by a mutation (Pro250Arg) of the *FGFR3* gene, with autosomal dominant inheritance and variable clinical expression (Doherty et al. 2007). Most cases are familial, but unless there is an index case in the family, the diagnosis may be missed in newborns with a mild phenotype.

Pfeiffer syndrome is a rare acrocephalosyndactyly caused by several mutations in *FGFR1* and *FGFR2* genes, with autosomal dominant inheritance and variable clinical expressivity. Premature fusion of the coronal sutures causes acrocephaly, frontal bossing, and flat occipital bone. Concomitant synostosis of sagittal and lambdoidal sutures may cause a cloverleaf appearance of the skull. The face is characterized by downslanting palpebral fissures, ocular proptosis, strabismus, hypertelorism, maxillary hypoplasia, and low-set ears. Hands and feet usually show hypoplasia of the first ray (large first finger and toe, trapezoidal toe) and various degrees of postaxial syndactyly. There may be associated elbow ankylosis or synostosis and vertebral fusions. Most severely affected patients require early surgical correction to prevent CNS complications. The prognosis is related to the degree of phenotypical expression.

Treacher Collins Syndrome (Franceschetti Syndrome)

This syndrome is characterized by a developmental defect of the jaw and facial bones.

There is wide variability. It is determined by several different mutations in the *TCOF1* gene (5q32) encoding the nucleolar phosphoprotein treacle, which has a key role in early craniofacial development, or in the *POLR1C* (6p21.1) or *POLR1D* (13q12.2) genes, encoding for RNA polymerase I and III subunits (Dixon 1996; Trainor et al. 2009). Neonatal features are downslanting palpebral fissures, palpebral coloboma, malar hypoplasia, macrostomia, micrognathia, external ear hypoplasia with atresia of the middle ear, and hearing loss. Cleft palate and choanal atresia may also be present. In the most severely affected patients, there may be impaired nutrition and respiratory function. Growth and psychomotor development are usually normal, but affected children need long-term multidisciplinary follow-up. Hearing loss requires early treatment to preserve speech development. Surgical treatment may correct bony defects and achieve useful functional and aesthetic advantages.

Nager Syndrome (Acrofacial Dysostosis Nager Type)

Nager syndrome is likely genetically heterogenous with confirmed autosomal dominant inheritance, but autosomal recessive inheritance is suspected based on sibling recurrence in consanguineous families. In approximately 50 % of patients, NAFD has been associated with heterozygous mutations in the SF3B4 gene (1q21.2), coding for a component of the splicing machinery (Petit et al. 2014). Patients have a mandibulofacial dysostosis with associated preaxial limb abnormalities (Fig. 10). The mandibulofacial dysostosis is mainly characterized by microcephaly, severe micrognathia and malar hypoplasia, low-set posteriorly rotated ears, and external auditory canal atresia. The limb deformities consist of radial aplasia or hypoplasia, radioulnar synostosis with limitation of elbow extension, and hypoplasia or absence of the thumbs.

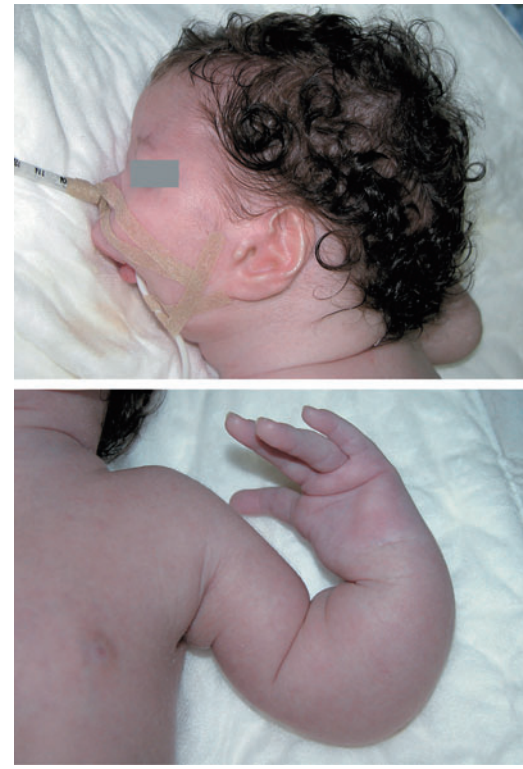

Fig. 10 Baby with Nager syndrome showing microcephaly, micrognathia, malar hypoplasia, and preaxial limb reduction defects

Thoraco-vertebral Dysostoses

Klippel-Feil malformation is a developmental defect of the spine, with possible changes at the cervical, thoracic, and/or lumbar level (short neck, pterygium, kyphosis, scoliosis). X-ray investigation of the spine is required to show vertebral changes (fusions, hemivertebrae, hemispondyls) and complete the diagnostic work-up; there are three clinical variants. It is more frequent in females. Its etiology is heterogeneous, with genetic and environmental (vascular disruptions) causes. It may also be part of a more complex phenotype (cervico-oculoacoustic syndrome, MURCS association).

Limb Dysostoses

Digital defects are caused by a differentiation defect of one or more contiguous bones. Digital

development is determined by a complex genetic system, which is phylogenetically common to most vertebrates. Digital anomalies may be sporadic or familial with Mendelian inheritance and may be associated with other digital defects (polysyndactyly) and other syndromic defects.

Polydactyly may be defined as the presence of one or more supernumerary fingers or toes. It is termed as complete if it involves all phalanges, partial if it involves only distal phalanges (duplication). In the preaxial forms, the extra digit is related to the thumb; in the postaxial forms, it is related to the little finger.

Syndactyly is the fusion of two or more digits: it may involve only the skin and muscle or include the bones. In the most severe cases, it may affect all the fingers of the limb causing a "spoon" appearance. *Symphalangism* is the fusion of one or more phalanges in the same digit, with severe ankylosis of the interphalangeal joint.

Brachydactyly is the shortening of a digit due to developmental defect of one or more phalanges. It is often associated with metacarpal or metatarsal hypoplasia.

Ectrodactyly is a severe developmental anomaly of the median axis of the hand or foot causing a "lobster-claw" appearance. It is usually caused by a genetic etiology and may be associated with other malformations (e.g., ectodermal defects and cleft palate in the ectrodactyly-ectodermal dysplasia-cleft syndrome [EEC syndrome]).

Oligodactyly is the absence or severe hypoplasia of one or more digital axes. It may be preaxial or postaxial and is frequently associated with other defects.

Osteochondrodysplasias

Osteochondrodysplasias are a wide and heterogeneous group of genetically determined conditions, involving the development and growth of bony and cartilaginous tissues. The bone involvement is often prenatally diagnosed, although some cases become evident after birth. The overall prevalence at birth is about 1/5,000. There has been a significant reduction in recent years because of ultrasonographic prenatal diagnosis of the most severe conditions. The classification of osteochondrodysplasias, based on phenotype, has recently been modified by advances in molecular genetics applied to genes involved in the synthesis of collagen and elastin, fibroblast growth factor receptors, cartilaginous proteins, vitamin D receptor complex, and lysosomal and peroxisomal enzymes.

Lethal osteochondrodysplasias are characterized by death during the perinatal period because of generalized involvement including long bones, spine, and cranial bones. Mortality is mainly related to respiratory failure (due to skeletal abnormalities and lung hypoplasia) and associated visceral and CNS malformations. Milder osteochondrodysplasias (with normal life expectancy, short stature, and abnormal bone development) may benefit from surgical bone elongation and other corrective surgery and rehabilitation programs.

Achondroplasia

This is the most common cause of disproportionate short stature with short limbs, determined by a heterozygous mutation (Gly380Arg) of the *FGFR3* gene at 4p16.3 which encodes a transmembrane receptor that is important in regulating linear bone growth, among other functions. It is inherited as an autosomal dominant trait with a high rate of de novo mutations (80–90 % of patients) and is related to advanced paternal age. The recurrence risk is low if parents are not affected. The phenotype at birth (Fig. 11) is characteristic: megalencephaly, frontal bossing, depressed nasal bridge, facial bone hypoplasia, prognathism, narrow thorax, rhizomelic short limb dwarfism, brachydactyly, trident hands, and hypotonia. Psychomotor development is normal. Patients frequently develop severe orthopedic complications (lumbar hyperlordosis). In some cases CNS complications, such as the cord compressions and hydrocephalus, may occur during childhood.

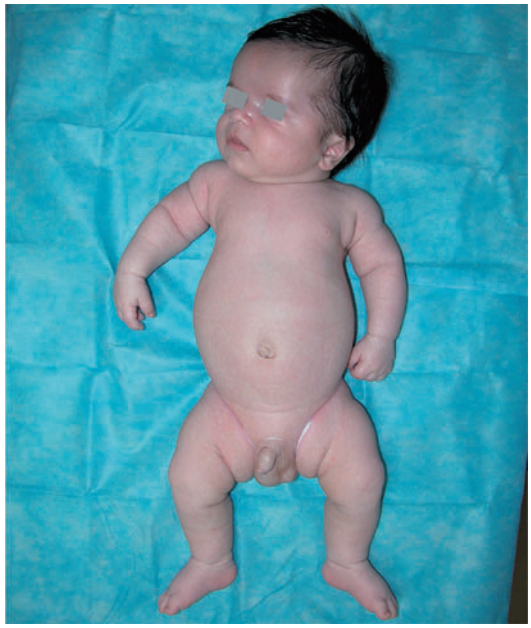

Fig. 11 Neonatal achondroplasia with rhizomelic short limb dwarfism, megalencephaly, frontal bossing, facial bone hypoplasia, and narrow thorax

Thanatophoric Dysplasia

Thanatophoric dysplasia (TD) is a severe and generally lethal skeletal dysplasia. The phenotype is characterized by severe micromelic dwarfism with bowing and deformations of long bones, "telephone receiver" femurs, narrow thorax, severe platyspondyly (flattening of the vertebral bodies), facial bone hypoplasia, and craniosynostosis. TD includes two forms: TD, type 1 (TD1) and TD, type 2 (TD2) that can be differentiated from each other by femurs (bowed "telephone receiver" femurs in TD1) and skull shape (cloverleaf skull is main reported in TD2). All patients are sporadic and due to de novo autosomal dominant mutations in the FGFR3 gene (4p16.3) which cause overactivity of the FGFR3 protein, resulting in the disturbances in bone growth and other tissues that are characteristic of TD.

Campomelic Dysplasia

Campomelic dysplasia is a severe autosomal recessive bone dysplasia with high perinatal lethality and female prevalence, due to mutations in the *SOX9* gene at 17q24. The phenotype includes sex reversal (female external genitalia with male chromosomes), macrocephaly, large fontanelles, broad depressed nasal root, micrognathia, short neck, pectus carinatum, short limb dwarfism, talipes, anterior bowing of tibiae, and poor ossification signs (Mansour et al. 2002).

Diastrophic Dysplasia

Diastrophic dysplasia is a rare autosomal recessive condition due to mutations of the *SLC26A2* gene at 5q31-q34 which encodes a sulfate transporter that is predominantly expressed in the cartilage. Mutations in the same gene have been implicated in a moderate form of epiphyseal dysplasia and in several lethal disorders such as achondrogenesis type 1b and atelosteogenesis type 2. The distinct morphologic abnormality of the growth plate consists of an irregular distribution of degenerating chondrocytes in the resting cartilage with areas of intracartilaginous ossification. Patients have rhizomelic short limb dwarfism, bilateral clubbed foot, cystic lesions of the pinnae with calcification of the cartilage, premature calcification of the costal cartilages, kyphoscoliosis, hip contractures, and cleft palate. The "hitchhiker" thumb is particularly characteristic and is due to a deformity of the first metacarpal. Intelligence is normal. Short stature with skeletal abnormalities becomes more marked with advancing age.

Pseudodiastrophic Dysplasia

Pseudodiastrophic dysplasia is an autosomal recessive condition described by Burgio in patients with a phenotype similar to diastrophic dysplasia but with proximal phalangeal joint dislocation, normal first metacarpal, platyspondyly, tonguelike lumbar vertebral deformities, and marked lumbar lordosis without cystic deformity of the helix (Fischetto et al. 1997). The histologic

appearance is different from diastrophic dysplasia and no *SLC26A2* mutations have been demonstrated. Most patients die during the first months of life.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a genetically and phenotypically heterogeneous group of conditions characterized by increased bone fragility, low bone mass, and susceptibility to bone fractures with variable severity (Bodian et al. 2009). Most frequently affected genes are those encoding for type 1 collagen (*COL1A1* on 17q21-q22 and *COL1A2* on 7q22) with autosomal dominant (AD) and autosomal recessive (AR) inheritance. Five different clinical variants have been differentiated, but only type 2 and type 3 are present at birth with a severe phenotype and high perinatal lethality:

- Type 1: AD, triangular face, blue sclerae, otosclerosis with secondary hearing loss, mitral valve prolapse, macrocephaly, joint hyperlaxity, and possible dental abnormalities
- Type 2: AD/AR, ossification deficiency, craniotabes, pseudohydrocephalic skull, micrognathia, small nose, blue sclerae, cardiac valve degeneration, endocardic and aortic microcalcifications, and multiple dental abnormalities
- Type 3: AD/AR, blue sclerae, hydrocephalus, cortical atrophy, joint hyperlaxity, shortness and bowing of limbs, and possible dental abnormalities
- Type 4: AD, macrocephaly, frontal bossing, hearing loss, joint hyperlaxity, osteoporosis, mild long bone deformations, and possible dental abnormalities
- Type 5: AR, mild to moderate short stature, dislocation of the radial head, mineralized interosseous membranes, hyperplastic callus, white sclera, and no dental abnormalities

Other genetically different types have been observed (types 6–9) but they are not clinically different from types 2 to 4.

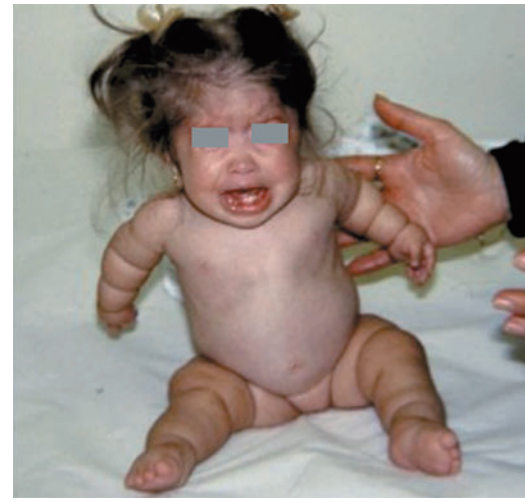

Fig. 12 Patient with osteodysplastic primordial dwarfism with microcephaly, severe shortness and deformations of long bones, and redundant skin folds at limbs

Osteodysplastic Primordial Dwarfism

Osteodysplastic primordial dwarfism is a group of brachymelic microcephalic dwarfisms with likely genetic heterogeneity and autosomal recessive inheritance. Different clinical variants have been described in patients with a prenatal onset of severe dwarfism (Fig. 12), microcephaly, delayed closure of fontanelles, prominent eyes and strabismus, microretrognathia, pointed nose, high-arched palate, oligodontia, small low-set dysplastic ears, sparse scalp hair, pectus carinatum, delayed bone age, severe osteoporosis, and multiple skeletal abnormalities (hip dislocation, coxa vara, joint contractures, short bowed long bones, small proximal femoral epiphyses, thin diaphyses of long bones, brachydactyly, talipes). Postnatal failure to thrive, mental retardation, sensory defects are consistently present during growth. Life expectancy is reduced.

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