



CLINICAL AND GENETIC APPROACH TO THE DYSMORPHIC CHILD

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*The child affected by a malformative syndrome represents a care challenge for the pediatrician. He is in fact the heart of the multidisciplinary team that has to manage the patient, trying to control the complications of his/her syndrome and promoting the correct psychophysical development. What we must not forget is that the pediatrician provides a continuous support to the child's family, assisting them from the diagnosis to the management of problems related to the syndrome. This encourages the continuous follow-up of these children remembering also that the pediatrician is fundamental in the clinical management of the syndrome and for facilitating the social integration of these children. **Biomed Rev 2018; 29: 37-46***

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INTRODUCTION

A birth defect, also known as a congenital disorder, is a condition present at birth regardless of its cause. Birth defects may result in disabilities that may be physical, intellectual, or developmental. The disabilities can range from mild to severe. The prevalence of birth defects is about 2-4% among live births (1, 2) which is the equivalent of about one patient out of 200 children with complex malformative syndromes and they are singularly considered rare diseases (3). It is calculated that the complex malformative syndromes

are approximately 8000, about a hundred of which have a prevalence between 1:2000 and 1:10.000; about 250 between 1:10.000 and 1:100.000, and about one thousand up to 1:1 million (4). The remaining 6500 represent sporadic cases. Therefore, because of the common genetic origin (80% of the cases), of the manifestation in pediatric age and the concomitant association with a form of disability, the complex malformative syndromes represent an important problem of public health (5, 6).

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Table 1. The prevalence of the most frequent genetic syndromes.

SYNDROME	PREVALENCE	SYNDROME	PREVALENCE
Down	1/800	Prader Willi	1/10.000
Klinefelter	1/1.200	Trisomy 13	1/10.000
Fra-X	1/2.000	Angelman	1/12.000
Noonan	1/2.000	Beckwith	1/14.000
Neurofibromatosis 1	1/3.000	Achondroplasia	1/15.000
Del22 (DiGeorge)	1/3.000	Williams	1/20.000
Trisomy 18	1/5.000	Saethre Chotzen	1/25.000
Turner	1/5.000	Poland	1/30.000
Tuberous sclerosis	1/5.800	Kabuki	1/32.000 (Jap)
VATER	1/7.000	Smith Lemli Opitz	1/40.000
Arthrogryposis multipla	1/10.000	Wolf	1/50.000
CHARGE	1/10.000	Apert	1/70.000
De Lange	1/10.000	Crouzon	1/80.000
Spondilocostal dysostosis	1/10.000	Cohen	1/100.000
Ehlers-Danlos	1/25.000	Holt Oram	1/100.000
Marfan	1/10.000	Sotos	1/10.000

Indeed, in Italy the period which goes from 0 to 18 years, age known as childhood-adolescence, includes roughly 10 million people. The 15 % of which, equivalent to 1.5 million, is represented by “children with special needs”, affected by chronic diseases which require a very demanding medical approach (7). Among this group of patients, about half (8% of the total, equal to 800.000 patients) are affected by diseases that involve disabilities, mental and physical defects that prevent social participation. These disabilities include different conditions such as: autism, infant cerebral palsy, consequence of tumors, but also diseases with elevated assistance demands as cystic fibrosis, thalassemia, spinal muscular atrophy and in the 0.5% of cases, equal to 50.000 patients, malformative syndromes like: Down, Cornelia de Lange and Noonan syndromes (8–10). These diseases can involve very serious clinical problems preventing personal autonomy, with important effects on assistance and social life. Hence in Italy in the last few years it was necessary to develop the branch of “Pediatrics of disability” which doesn’t only involve the multispecialized medical approach, but is enhanced by multisectorial approaches which

includes educational, scholastic and social features extended to the whole territory (11). Such an approach should be achieved through the creation of an assistance network which should integrate the reference group for rare diseases, which should create the assistance program and the family pediatrician, who should participate to the whole program (4).

What is the role of the family pediatrician in this integrated assistance network? For sure it’s a fundamental and comprehensive role, which goes from the possibility of suspecting a disease to the management of its clinical requirements in collaboration with the reference group. In addition, the family pediatrician should identify the social needs of the child, understand the emergency and report the cases that need a rehabilitation (12, 13).

In other words, he could be the person responsible for the territory, who works in close touch with the family to facilitate the access to all the medical and social services (4). These services should completely satisfy the needs of the child and his family to facilitate the participation of the child to the social life in the best way possible (13).

THE PEDIATRICIAN MEETS THE CHILD WITH A MALFORMATIVE SYNDROME

The pediatrician can do this in several ways:

- 1 When, among his patients, the pediatrician meets a newborn with a specific diagnosis. In this case the child already has a label, apart from the physical problems associated with chronic diseases, this can include specific aspects of the genetic syndromes. Among these there are the fear that the child will be discriminated because of his condition and the possibility of a difficult interaction between child and parents (13). Other important aspects are: the prognosis *quoad vitam* and *quoad valetudinem*, the implementation of an assistance program, the genetic consultation to investigate the family's history, the certification of rare disease and the contact with a parent's association to receive psychological support (4). Therefore, it's important that the pediatrician acquires as much information on the condition of the child especially on the variation of the medical situation, possible complications and follow-up (14). It would be useful to make sure the family has correctly understood the disease of the child and if not the pediatrician should refer the parents to the center which drew up the diagnosis (4). It would be also useful for the doctor to carry out a careful pediatric examination in order to treat the child like a normal patient, having periodic evaluations of height's and weight's growth by using, if available, the percentiles related to the specific syndrome. It would be wise to introduce a correct diet, for example hypocaloric in the Prader-Willi syndrome and hyper caloric in the Costello syndrome, and propose the optional vaccinations which don't have side effects from the beginning (15, 16). In fact, vaccinations are quite useful considering the high risk of respiratory infections in children with congenital heart disease, dysphagia/gastroesophageal reflux or restrictive pulmonary disease due to ribs abnormalities (17). The pediatrician must constantly follow in which way the family tackles the problem and the efficiency of the assistance network.
- 2 When the newborn arrives without a diagnosis, but instead with one or more major malformations (18–20). The pediatrician can be a valuable support to the family in the identification of the disease, knowing that even without a diagnostic label, the single problems can be faced in the same way.
- 3 When a normal child begins to show abnormalities in the psychomotor development or growth problems. The pediatrician should understand if the abnormality is isolated or associated with other malformations (21). For this reason,

it's important that he prescribes blood test, radiological studies and functional tests like electroencephalogram, electrocardiogram, audiometric and oculist examination to reveal possible problems.

- 4 When he himself draws up the diagnosis of malformations or functional problems (visual, auditory, neurological, cardiac, renal) after the neonatal period. He should also document the clinical problems and his own diagnostic suspicion, directing the child to the geneticist. Apart from this he should explain why is sending the child to the geneticist and the possible diagnostic process (18, 20, 22–26). At this point the pediatrician should inform the parents about the limits of the diagnostic process, in fact his suspicion could be erroneous or else it isn't possible to draw up a perfect diagnosis (13).

WHEN AND HOW CAN THE SYNDROME BE SUSPECTED

The clinical approach to the malformation syndromes presents peculiarities because of the clinical, etiological and pathological variations. The first thing is to present a diagnostic suspicion which precedes the clinical analysis, but demands especially attention on the part of the pediatrician (18).

The clinical elements which led to suspect a malformation syndrome are four: the presence of facial dysmorphisms such as hypertelorism, proptosis, oblique rima palpebrarum upwards or downwards, short nose with antiverse nostrils, long philtrum micrognathia and ears in a lower position (18). These details give the face a very particular aspect, in fact these patients don't resemble any member of the family.

The presence of major or minor malformations variably associated between themselves (18). In fact, an anorectal abnormality is syndromic in 50% of the cases, the cleft palate in the 30%, an heart congenital disease or cataract in the 20% and a kidney malformation in the 15% (27). Some malformations are typical of specific syndromes such as tongue's hamartoma in the oro-facial-digital syndrome, the pulmonary stenosis valve in Noonan syndrome, the stenosis above aortic valve and the stenosis of pulmonary arteries in Williams syndrome, an heart disease and cleft palate in DiGeorge syndrome and the duodenal stenosis in Down syndrome (8, 10).

The presence of growth problems, either in excess (gigantism) or in default (dwarfism) or the presence of different between head and torso, torso and limbs, between the limbs themselves or between hemisomes (28). The abnormalities can also involve the skull such as macrocephaly (Sotos syndrome, hydrocephalous), and microcephaly which is evident at birth as in the Fetal Alcohol Spectrum Disorders (FASD; see Carito et

al's "FASD in Pediatrics" in this volume of *Biomedical Reviews*) or in the Seckel syndrome, or else this can appear at a later period as in the Angelmann syndrome or in the Rett syndrome (29–32).

The presence of delayed psychomotor development, especially if associated with sensorial problems, is probably linked to a syndrome (21). If congenital abnormalities appear at birth it's the job of the neonatologist to assess them, but after that it will be responsibility of the pediatrician to identify defects in psychomotor development (33). The pediatrician will have also to consider major malformations in a child appearing normal at birth or else if the child had only one single malformation. Indeed, it is important that the pediatrician confirms that the abnormality is isolated or associated with a syndrome.

Then it will be the geneticist job to understand the etiology of the syndrome throughout a process composed of various elements which tend to complement each other, but which can also lead to diagnosis if considered separately. Therefore, there are two roads to follow in order to reach the diagnosis: the *gestalt* diagnosis and the analytical diagnosis. The first one, at a glance, consists in the immediate recognition of a well-known phenotype, and benefits itself of the association

between memory and experience like recognizing a friend among a crowd. The diagnostic suspicion must then be confirmed by analytical instruments.

The analytical diagnosis, instead, uses the classical medical instruments such as: the family's history (genealogical tree of at least three generation to identify genetic diseases), the gestational history (threat abortion, quantity of amniotic fluid, growth and movements of the fetus, infections, abuse of alcohol and drugs, tobacco, prenatal diagnosis), neonatal history (asphyxia), physical examination, instrumental and clinical analyses associated to computer systems (POSSUM scoring system, London Dysmorphology Database) (21, 34).

Then it is up to the geneticist to define the case under observation, even utilizing further checks to find elements which are compatible with the disease, and prescribing genetic tests. The recent development of genetic testing, with an estimated detection rate of 40% for Next Generation Sequencing (NGS) and of 10% for microarrays analyses, allows to perform an etiological diagnosis in at least half of the known syndromes: Williams syndrome 95%, Sotos syndrome 90%, Noonan syndrome 80%, Cornelia de Lange syndrome, Kabuki syndrome and CHARGE syndrome 70%. (9, 10, 29, 35–37).

Table 2. The clinical and genetic characteristics of the most common genetic syndromes (7, 8, 13, 23, 25, 29, 31–46).

SYNDROME OR ASSOCIATION	MAIN SYMPTOMS	GENETIC MUTATION
Achondroplasia	Poor growth with short arts, brachydactyly, macrocephaly, and facial dysmorphisms	Genetic mutation in the FGFR3 in 4p16.3
Neurofibromatosis 1	Cafe-au-lait spots, eye hamartomas (Lisch nodules), neurofibromas, skeletal abnormalities, optic nerve glioma	Mutation or deletion in the NF1 gene in 17q11.2
Angelman	Facial dysmorphisms, microcephaly, developmental delay, language's problems, epilepsy	Lack of function of 15q11.2 inherited from mother
Apert	Craniosynostosis, facial dysmorphisms, syndactyly of hands and foot	Mutation in the FGFR2 gene in 10q26.13
Bardet Biedl	Obesity, mental disability, polydactyly post-axial, nephropathy, hypogonadism, retinopathy	Mutations in 12 different genes
Beckwith Wiedemann	Overgrowth, umbilical hernia, omphalocele, macroglossia, hemihyperplasia, visceromegaly	Mutation or deletion of imprinted genes in the area 11p15.5 (H19,KCNQ10T1,CDKN1C)
Crouzon	Craniosynostosis, facial dysmorphisms	Mutation in the FGFR2 gene in 10q26.13
Marfan	Above height and disproportionately long limbs (dolichostenomelia), ectopia lentis, aortic aneurysm or dilatation, mitral valve prolapse	Mutation in the FBN1 gene in 15q21.1

SYNDROME OR ASSOCIATION	MAIN SYMPTOMS	GENETIC MUTATION
Prader-Willi	Facial dysmorphisms, hypotonia, small hands and foot, hypogonadism, obesity, hyperphagia, short stature, neurodevelopmental delays	Lack of function of 15q11.2 inherited from father
Rubinstein-Taybi	Facial dysmorphisms, growth's problems, neurodevelopmental delays, wide and bifid thumbs or toes	Microdeletion in the 16p13.3 area, and mutation in the CBBP gene in 16p13.3, mutation in the EP300 gene in 22q13
Sotos	Overgrowth, increased bone age, facial dysmorphisms, delayed psychomotor development	Mutation or deletion in the NSD1 gene in the area 5q35 in (70% of patients)
Cri du chat	Microcephaly and mental disability	Deletion of a part of 5p
CHARGE	Coloboma, congenital heart diseases, Choanal atresia/stenosis, lack of growth, genitals abnormalities, hypoacusis, auricle abnormalities	Mutation in the CHD7 gene in 7q21.11, mutation in the SEMA3E gene in 8q12.1-q12.2
Cornelia De Lange	Facial dysmorphisms, lack of growth, neurodevelopmental delays, hirsutism, small hands and foot	Mutation in the NIBL gene in 5p13.1, mutation in the SMC1L1 gene in Xp11.22-p11.21, mutation in the SMC3 gene in 10q25
Di George	Facial dysmorphisms, congenital heart disease, hypocalcaemia, immune deficiency, neurodevelopmental delays, cleft palate, suction's and swallowing's difficulties	Microdeletion of 22q11.2
Holt-Oram	Heart congenital diseases (or ECG abnormalities), abnormalities of unilateral upper limb	Mutation in the TBX5 gene in 12q24.21 (30% of patients)
Noonan	Facial dysmorphisms, short height, pulmonary stenosis, pterigium colli, pectus excavatum/carenatum	Mutation in the PTPN11 gene in 12q24.1 (50% of patients), mutation of RAS-MAPK's pathway (KRASS, SOS1, NRAS, RAF1 genes)
Silver Russell	Poor growth, asymmetry of limbs and face, facial dysmorphisms, disproportion between braincase and facial skeleton	Maternal upd (uniparental disomy) of chromosome 7 in the 10% patients, hypometilation of H19 gene in 11p15 (30% of patients)
Treacher Collins	Facial dysmorphism, variability of clinical signs	Mutation in the gene TCOF1 in 5q32-q33.1, mutation in the gene POLR1C in 6p21.1, mutation in the gene POLR1D in 13q12.2
Williams	Facial dysmorphism, aortic stenosis, neurodevelopmental delays, friendly character	Microdeletion 7q11.23
Wolf-Hirschorn	Facial dysmorphism, short growth, neurodevelopmental delays, eyes, renal and neurological malformations	Deletion of 4p16.3
Goldenhar	Asymmetry of the face, microtia or unilateral abnormality of the auricle, preauricular appendages, epibulbar dermoid and vertebral abnormalities	Clinical diagnosis
VATER/VACTERL	Vertebral and anal abnormalities, esophageal atresia associated to tracheo-esophageal fistula, renal malformations, heart congenital malformation	Clinical diagnosis

THE ASSISTANCE AFTER THE DIAGNOSIS

Immediately after the establishment of a diagnosis, etiological or genetic, or even in the absence of this the doctor takes control of the syndromic child; starting from the evaluation of his initial abilities (functional diagnosis) (53). At this point the pediatrician asks himself what the child will be able to do? What he will be able to do if he is helped? What can be corrected? What can be foreseen? All this to program the best clinical and rehabilitation follow-up (12). “The work of the pediatrician should come out of the clinic and be extended to all which is connected to the child’s life” (54). Therefore he can intervene on the child, but he must also consider the economic, environmental and social situations of the family; furthermore the pediatrician can provide indications regarding medical education, he should also anticipate possible problems and perform preventive actions (13, 26).

For this he must be familiar with the syndrome having knowledge of the course, of possible complications, of emergencies and also the handling of the devices such as percutaneous endoscopic gastrostomy feeding, central line or tracheostomy (55, 56). The doctor should guarantee the correct nutritional intake of the child, by monitoring the intake of calories, the growth parameters and evaluating the possible vitamins and electrolytic deficits produced by feeding problems or drugs (57).

The supplements of vitamins and fluorine must follow the same guidance of the healthy children (58). Due to the risk of a possible impaired food deglutition the pediatrician must diagnose dysphagia and gastro-esophageal reflux, in order to begin a rehabilitation or a medical therapy, before directing the child to a specialist (12). The sleeping habits must be evaluated in order to direct the child to a specialist to solve problems (59).

Vaccinations must be done also on disabled children because they are more exposed to respiratory diseases, even if the vaccines coverage today is very low in this children (17). Finally, the pediatrician must assess if the family receive a proper social support, discover if the child is harmoniously integrated in the school environment, if he his carrying out his rehabilitation and if there is interaction between the facilities that assist him (12, 26). The pediatrician must guarantee the emergency’s handling of the child with syndrome. This because these children enter the emergency room twice more than healthy children and are hospitalized much more easily (60). At the base of this, on one hand, there is the mistrust of the families towards the local clinics, but on the other hand, also the pediatrician is concerned about the fragility of the child.

Therefore, the knowledge of the course of the syndrome

could facilitate the diagnosis of the complications and limit hospitalization to really deserving cases. In some of these syndromes there are specific symptoms that can lead to an immediate diagnosis such as chest pain in a boy with Marfan syndrome to suggest a pneumothorax or aortic dissection (38). While the abdominal pain in Williams syndrome should suggest an intestinal or a bladder diverticulitis or a mesenteric ischemia. On the contrary, in the Cornelia de Lange syndrome could suggest a volvulus due to intestinal malrotation and in Ehlers Danlos syndrome could indicate an intestinal rupture (9, 35). For example the headache in Williams syndrome and in Neurofibromatosis type 1 must orientate towards an hypertensive crisis or a cerebral stroke; while the sudden hypotonia/hemiplegia in Down syndrome, achondroplasia and in the mucopolysaccharidosis must orient towards a trunk-encephalic compression from atlanto-axial instability (8, 35, 52, 61).

CONCLUSION

Even if the child with a malformative syndrome could not fully recovered, thanks to the abilities of the pediatrician he can be cured in the best way possible to improve the quality of the patient life and also for potentiating the child social integration (13).

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in this review article.

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