CORSO INTEGRATO DI GENETICA
AA 2010/11

Prof Alberto Turco

Gio 2 dicembre 2010

Lezioni 49 e 50

GENETICA CLINICA
DISMORFOSIOLOGIA
1.2. BIRTH DEFECTS

About 3% of all the children born in any hospital or in any country or in any year will have a significant congenital abnormality—one which is of more than cosmetic concern and which, uncorrected, will interfere with normal functioning (Fig. 1.1A). Although such anomalies occur in only a small fraction of all newborns, they cause a much larger proportion of neonatal and infant deaths, and children with birth defects make up about 30% of all admissions to pediatric hospitals. Furthermore, these problems appear, by definition, at the very start of life, and many affected individuals require chronic care for decades. The burdens imposed on these people, their families, and society at large are enormous. As yet, the great majority of birth defects are neither detectable by prenatal diagnosis nor preventable, and thus the impact of these problems has not decreased despite all the advances in other areas of pediatric medicine.

Almost all birth defect syndromes are exceedingly rare, and a practicing physician would be expected to see only a handful of such cases in his or her professional lifetime, yet there are so many different disorders that even a specialist in the field will never gain experience with all of them. Therefore, the approach set forth here depends not on rote memorization of the features of rare syndromes but on recognition and analysis of their component anomalies.

For purposes of conceptualization as well as for ease of discussion, it is helpful to divide birth defects into those affecting one or several organ systems (Fig. 1.1B). A further

J. M. Aase, "Diagnostic Dysmorphology"
Plenum Medical Book Company, 1996
Tabella 1: Anomalie congenite: classificazione e stima dell'incidenza e dell'esito annuo delle gravidanze in Europa (nascite annue totali ≈ 13.6 × 10⁶)

<table>
<thead>
<tr>
<th>Categoria anomalie</th>
<th>Numero per 1000 nati vivi</th>
<th>Nascite per anno</th>
<th>Malattia normale</th>
<th>Inf全日制</th>
<th>Transamnio effettivo</th>
<th>Principali anomalie terapeutiche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multipli anomalie</td>
<td>30.0</td>
<td>280 000</td>
<td>89 000</td>
<td>22</td>
<td>98 000</td>
<td>24</td>
</tr>
<tr>
<td>Anomalie</td>
<td>3.2</td>
<td>14 000</td>
<td>14 000</td>
<td>34</td>
<td>28 000</td>
<td>44</td>
</tr>
<tr>
<td>Malattia congenita</td>
<td>7.0</td>
<td>55 000</td>
<td>55 000</td>
<td>58</td>
<td>29 000</td>
<td>11</td>
</tr>
<tr>
<td>Totale</td>
<td>40.2</td>
<td>197 000</td>
<td>197 000</td>
<td>58</td>
<td>135 000</td>
<td>58</td>
</tr>
</tbody>
</table>

Oltre 20 milioni di bambini su 13 milioni (1.4%) nati in 1 anno presentano una grave anomalie congenita.

Tabella 14.3: Cause di difetti congeniti

<table>
<thead>
<tr>
<th>Eziologia</th>
<th>Prevalenza %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetica</td>
<td>30-40</td>
</tr>
<tr>
<td>- Cromosomica</td>
<td>6</td>
</tr>
<tr>
<td>- Mendeliana</td>
<td>7,5</td>
</tr>
<tr>
<td>- Multifattoriale</td>
<td>20-30</td>
</tr>
<tr>
<td>Ambientale</td>
<td>5-10</td>
</tr>
<tr>
<td>- Farmaci e agenti chimici</td>
<td>2</td>
</tr>
<tr>
<td>- Infezioni</td>
<td>2</td>
</tr>
<tr>
<td>- Malattie materni</td>
<td>2</td>
</tr>
<tr>
<td>- Agenti fisici</td>
<td>1</td>
</tr>
<tr>
<td>Cause non note</td>
<td>50</td>
</tr>
</tbody>
</table>
Although far less dramatic than legionnaire's disease, toxic shock syndrome, or AIDS, severe congenital birth abnormalities are far more common, affecting two to four infants in every 100 births. Thus, in aggregate and over many years, birth anomalies have a great impact on our economy. And surely they generate considerable emotional erosion. Yet apart from the National Foundation March of Dimes, there have been few large organizations that have supported investigation of birth anomalies, and none has been concerned with the training of dysmorphologists.

The dysmorphologist or syndromatologist is often thought of by other clinicians as being lost in arcane details, obsessed with minutiae, speaking in tongues beyond the realm of professional comprehension, understood by none except those similarly engaged. On the other hand, the consulting family perceives the dysmorphologist as one who knows all, who will provide a diagnosis and answer all questions about prognosis and therapy. In truth, neither of these views is correct.

There is probably no other area of endeavor in which failure to diagnose is accepted as the norm. Could one practice surgery or civil engineering or law and fail so often, yet be considered an expert? Under no circumstances! Nevertheless, it has been demonstrated repeatedly that the best of us has no greater than a 20% overall rate of success. Surely it must be the only field in which one can perform so dismally yet be considered competent.

There is something metaphysical about naming a disorder. All concerned—the patient, the clinician, the parents—seem to experience a certain satisfaction or sense of security when an unknown condition is defined. This is valid, since understanding has its incipience in definition. The unknown is scary. Once the condition has been measured and its extent limited, its recognition is made easier. Thereby, interest and concentration can be more easily focused upon it. This, in turn, may lead to therapy and control.
Reaching a diagnosis in a child with congenital abnormalities bears many similarities to the work of a detective in solving a crime. The physician is confronted with the end product of events that took place weeks or months before, unseen and usually unsuspected. He must use every available physical clue, together with the testimony of “witnesses,” to try to reconstruct the crime. If he can solve the mystery and identify the cause of the malformation, he can provide invaluable help for the victim and his family. In some rare instances, the “culprit” can be permanently removed from circulation, as in the case of thalidomide and, it is to be hoped, rubella.

Surely the fictional archetype for observation and deduction is Sherlock Holmes. His uncanny ability to construct logical chains of reasoning from the most obscure evidence has made his name synonymous with the word “detective.” I heartily recommend the stories of Arthur Conan Doyle as bedtime reading for anyone interested in the art and science of observation. A number of quotations from these works have been inserted at appropriate places in this text, not so much as “comic relief,” as to emphasize the value of certain general principles in the diagnosis of dysmorphic conditions.

While the detective analogy should not be stretched too far, the principles of careful data gathering, minute observation of subtle physical clues, and deductive reasoning do form the basis of dysmorphologic diagnosis, and these techniques are incompletely addressed in textbooks of physical examination and compilations of birth defects “syndromes.” This book is intended to describe the methods used by dysmorphologists to gather clues from the history and physical examination and to outline the reasoning processes used to reach a meaningful diagnosis. It is intended primarily for the instruction of house officers, fellows, and practicing physicians, and assumes a background in clinical medicine and, particularly, pediatrics.

Albuquerque, New Mexico

Jon M. Aase

1.1. EMBRYOLOGY

1.1.1. Developmental Timing

Prenatal development may be conveniently divided into three time periods: the implantation stage, extending from the time of fertilization of the egg to the end of the third week of gestation, the embryonic stage, from the beginning of week 4 to the end of week 7, and the fetal stage, from week 8 until birth.

During the implantation stage, rapid cell proliferation leads to the formation of the hollow blastocyst, within which develops the embryonic plate. The amniotic cavity appears, and primitive circulatory connections with the placenta are established. Early cell differentiation begins late in this period, with somites demarcated in the mesodermal layer, and longitudinal folds of neuroectoderm indicating the site of the future brain and spinal cord.

The embryonic stage is the time of primary tissue differentiation and the formation of definitive organs. Neural tissues undergo very rapid proliferation, with closure of the neural tube and flexion of its anterior segments to form the divisions of the developing brain. The heart begins to beat, allowing blood to circulate through the newly formed...
Errori della morfogenesi

Sviluppo normale

Malformazione
diffetto intrinseco
morfogenesi di un organo (es: ciechissimo, VTB) (contro 8° sig. ciechina organogenesi)

Distruzione
danno di un tessuto/organio
gliemiato da cause esterne (es. blasto
diuretico, subcutanea, quimioterapia, eruzioni cutanee)

Deformazione
sviluppo anomalo di una struttura
conflitto di forze esterne e interna concavità
doppi scottamenti, malforma, SUL, sindrome della distrofia
dopo 8° seg. es: piedi tondi

Classifica della classificazione di birth defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Examples</th>
<th>Causes and genetic implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifactorial</td>
<td>Cleft lip/palate</td>
<td>Most isolated malformations show multifactorial inheritance</td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>Neural tube defects</td>
<td></td>
</tr>
<tr>
<td>Disruption</td>
<td>Craniofacial clefts caused by congenital rubella</td>
<td>Caused by environmental factors, recurrence risk is usually very low</td>
</tr>
<tr>
<td>Limb defects caused by amniotic bands</td>
<td>Congenital hip dislocation</td>
<td>Caused by mechanical compression, recurrence risk depends on cause</td>
</tr>
<tr>
<td>Deformation</td>
<td>Talipes (club foot)</td>
<td></td>
</tr>
<tr>
<td>Anomaly</td>
<td>Skeletal dysplasias, e.g. achondroplasia</td>
<td>Often caused by single gene defects</td>
</tr>
<tr>
<td>Abnormality</td>
<td>Potter (oligohydranios) sequence</td>
<td>Usually sporadic with low recurrence risk</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Cleft palate, Down syndrome, fetal alcohol syndrome</td>
<td>Can be chromosomal, single gene or non-genetic</td>
</tr>
<tr>
<td>Association</td>
<td>VATER association (vertebral, anal, tracheo- esophageal and renal abnormalities)</td>
<td>Not genetic, although cause is not known</td>
</tr>
</tbody>
</table>

Medical Genetics
Ian D. Young
Oxford Univ Press, 2005
Difetti Congeniti (Birth defects)
(Malformazioni congenite)

- **Maggiori**
  - intervento chirurgico
  - cardiopatia (E.H., anomalia renale)
- **Minori**
  - lesioni congenite
    - neurologiche
    - oncolitiche

**Incidenza:**
- Difetti maggiori alla nascita...2-3\%
- Difetti minori...10\%
- Totale 15\%

**Mortalità infantile** (5% entro 1 anno)

**Nel 50% dei casi: cause ignote**

- anomalie vascolari
- mutazioni mendeliane
- altri: base residua di regredenza, asimmetria delle lesioni

D. c. isolato? cercarne altri...
**Deformation (Secondary effect)**

- Compression or biomechanical distortion of an already normally formed body part which usually occurs after 8 – 10 fetal weeks

Ex: club feet, plagiocephaly, torticollis, contractures, dimples, joint dislocations
Disruption (Secondary defect)

- Compression / biomechanical distortion of an already formed (or to be formed) normal body part to such an extreme that the resulting defect looks like an anomaly

Ex: oligodactyly due to amniotic bands, cleft palate due to glossoptosis; web neck due to nuchal edema
Major Anomaly

- Basic alteration in embryological development severe enough to require intervention and which potentially has a long-term impact medically and/or psychologically

Example: spina bifida, omphalocele, bilateral cleft lip/palate, anophthalmia

Anomaly (Primary Defect)

- Basic alteration in structure of a body part usually occurring by 8 – 10 fetal weeks

Examples: cleft lip, phocomelia, anencephaly
NTD
Neural Tube Defects

NB: Folati!!!
NDT Encefalocele

NDT Anencefalia
Labioschisi (labbro leporino)
Labiopalato schisi
Minor Anomaly

- Basic alteration in embryological and/or fetal development which requires no treatment or can be, more or less, corrected

Ex: postaxial polydactyly, absent digital flexion creases, low-set ears, preauricular tag

Minor anomalies
Polidattilia

Minor / Normal Variant Feature

- Low frequency (1% - 5%) congenital feature found in the normal population or as an integral part of a multiple congenital anomaly syndrome

Ex: simian line, 5th finger clinodactyly, 2-3 toe syndactyly, epicanthal fold, accessory nipple
Multiple Congenital Anomalies (MCA)

- Two or more structural primary defects in two or more body areas, or in embryologically different areas
- Usually associated with a potentially recognizable syndrome
Syndrome

- Recurring pattern of structural defects and/or secondary effects/defects that allow for secure recognition
- Combination of features most likely represents a specific etiology
Sequence

- A situation where a single event (usually undefined) leads to a single anomaly (or situation) which has a cascading effect of local and/or distant deformations and/or disruptions.
Tabella 14.7 – Esempi di agenti fisici a rischio per il feto

Agente – Effetto

- radiazioni ionizzanti, dosi elevate – microcefalia, difetti oculari, nuove mutazioni, tumori
- calore/iperplessia elevata e protratta – difetti del tubo neurale, altri difetti del SNC, ritardo mentale
- oligoidramnios/gravidanze gemellari/ malformazioni uterine – deformità da posizione, difetti in riduzione degli arti, ipoplasia mandibolare
- bande amniotiche – sindattilia, amputazioni degli arti, schisi facciali atipiche, encefalocele, toraco-gastrochisisi, difetti oculari
Tabella 14.8 - Esempi di patologie metaboliche e genetiche materne, a rischio per il feto

**Fattore di rischio – Effetto**
- *Diabete mellito insulinodipendente* – cardiopatie, difetti del tubo neurale, renali, schisi facciali, oloprosencefalia, sindrome da regressione caudale
- *Distrofia miotonica* – distrofia miotonica ad esordio connatale, artrogriposi, cardiopatie, cataratta, ritardo mentale
- *Fenilcetonuria* – ritardo mentale, ritardo di crescita, microcefalia

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**Natimortalità**

- Cause genetiche
  - Cromosomiche 5-10%
  - M. mendeliane (e. nondisc. letali: OI, DT, acnuegenosi)
- Cariotipo neonato (sangue o fibroblasti)
- Fotografie e R.X!
- E.ame autopsico
- Conservazione campioni biologici (da retrospettiva)
Tabella 2.9: Prevenzione primaria e secondaria dei difetti congeniti

<table>
<thead>
<tr>
<th>Prevenzione primaria (fase pre-concezionale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuare e correggere affezioni materni potenzialmente responsabili di difetti congeniti: diabete, endocrinopatie, epatopatie, ecc.</td>
</tr>
<tr>
<td>Sintesi di complessi TORCH. Vaccinazione soggetti non immuni (neonati) e consigli circa le misure igieniche atte a prevenire altre infezioni</td>
</tr>
<tr>
<td>Informare circa gli effetti teratogeni di alcuni farmaci</td>
</tr>
<tr>
<td>Dovutamente da stili di vita non idonei in gravidanza (fumo, alcool, droghe, ecc.)</td>
</tr>
<tr>
<td>Consigliare l'utilizzo di acido folico in età preconcezionale e nella fase organogenetica</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevenzione secondaria (fase post-concezionale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osservanza scrupolosa delle norme di igiene della gravidanza, con particolare attenzione all'alimentazione</td>
</tr>
<tr>
<td>Realizzazione di programmi di screening ecografici e bioclinici dei difetti congeniti nella popolazione non a rischio</td>
</tr>
<tr>
<td>Diagnosi prenatale invasiva dei difetti congeniti</td>
</tr>
<tr>
<td>Monitoraggio accurato della gravidanza a rischio</td>
</tr>
</tbody>
</table>