Congenital Malformations

6

6.1 Definition

There is no generally agreed-upon definition of a congenital malformation. It should involve a structural abnormality which has developed during intrauterine life. Inborn errors of metabolism, nearly always genetically caused, without structural abnormalities should therefore not be included. The same is true for some other birth defects like congenital cerebral palsy or mental retardation without a structural background, but a structural congenital malformation may cause mental retardation. The concept of structural abnormality is not well defined. How much should a "malformed" individual differ from the "normal" individual? Variations for instance in external ear morphology or the presence of a four-finger line in the hand are no congenital malformations but normal variants even though both are overrepresented for instance in individuals with Down syndrome. Nevus is really a skin malformation but practically all of us carry nevi. A restriction to more severe conditions is needed but will be somewhat arbitrary. Can a morphologically patent oval foramen in the heart (which is a very common phenomenon, perhaps in 25 % of all individuals and usually without any clinical significance) be regarded as a malformation? The normal closure has actually not taken place, and the condition can under rare circumstances cause problems and may have to be surgically corrected.

Minor variants should not be included in the concept of congenital malformations, but the definition will be vague. If many variants are present simultaneously, this may indicate a disturbed morphogenesis. We have already mentioned that some variants are more common at Down syndrome than in the population, and there is a list of further such signs. Such phenomena are often called dysmorphology, and characteristic signs have been described after maternal abuse of alcohol (fetal alcohol syndrome, FAS) or after maternal use of some anticonvulsants, first described by Bénthenod and Frédérich (1975), Seip (1976), and Hansson et al. (1976). In order to identify dysmorphology, a qualified examination of the child by a specialist is needed. This is usually relevant only in small studies of specific drugs and should be made "blind" as the evaluation is somewhat subjective.

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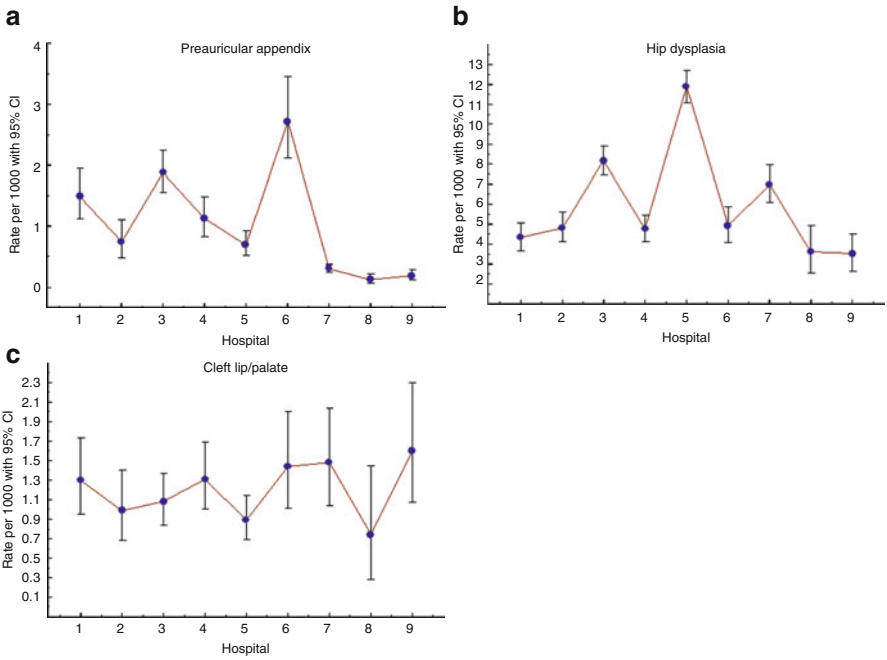

Fig. 6.1 Diagrams showing variation in registered rates of two minor (preauricular appendix (**a**) and hip dislocation (**b**)) and one major (cleft lip/palate (**c**)) malformations in nine teaching hospitals. Hospitals 1–4 are all Stockholm hospitals

Also among conditions which are usually called congenital malformations, there exists a marked variability in severity and some are of relatively modest clinical significance. Often a distinction is made between "major" and "minor" malformations, and analyses are often restricted to major ones. There are two reasons for this. One is that the minor ones make up a substantial part of the total and can hide effects on major malformations; the other is that there is a much higher variability in the reporting of minor malformations than of major malformations. This can be illustrated by data from Sweden where information on congenital malformations is collected from multiple register sources. In Fig. 6.1 the rates of three malformations are compared between nine large hospitals (10,000–70,000 births during the observation period 2005–2013). Two malformations are minor (preauricular appendix and hip dysplasia); one is major (cleft lip or cleft palate). A large variation in rates is seen for the first two conditions while the variability for the third is much less and may be random.

6.2 Major and Minor Malformations

A common definition of a major malformation is that it should be potentially lethal, need surgery or other treatment, or give major cosmetic problems. For many conditions, this definition is quite adequate (e.g., spina bifida, major heart defects, cleft

lip/palate, limb reductions), for others it is more difficult to use the definition. Postaxial polydactyly needs surgery but it is often a very quick and minor operation, and the malformation is therefore sometimes not counted as major.

If the description of the malformation is detailed, it is usually possible to classify it as major or minor. If only ICD codes are available – which is often the case in large register studies – it is more difficult and sometimes nearly impossible to evaluate the severity of the malformation, notably when the code marks "other" or "unspecific" malformations, for example, ICD-10 codes Q55.8 = "Other specified malformations of male genital organs" or Q55.9 = "Congenital malformations of male genital organ, unspecified." A code indicating a ventricular septum defect (Q21.0) may represent a heart malformation which will need surgery or a defect which closes spontaneously and which will never play any role.

In the European congenital malformation-monitoring organization (EUROCAT), lists of malformations which should be regarded as major or minor are given. To use them, more detailed information is often needed than what is given by the standard ICD-10 code.

According to my view, the important thing is to eliminate minor malformations by removing from the analysis common and variably registered conditions in order to get a more stable concept. Since many years we have in Sweden used a method of excluding such conditions and we have called the remaining ones "relatively severe," in practice it will be rather similar to what is usually called major malformations, but among them will some minor conditions be left. It will, however, reduce the variability in recording as was evident above. The conditions which are excluded are preauricular tags, patent ductus arteriosus in preterm infants, tongue-tie, single umbilical artery, undescended testis, hip dysplasia, and nevus. These exclusions reduce the rate of malformations from about 5 to about 3 %. This leaves, for instance, preauricular pits which EUROCAT classifies as minor, but it is a condition which often needs surgery.

6.3 Single and Multiple Malformations

Infants may have more than one code for a congenital malformation. Experience has shown that teratogenic agents often give more than one malformation and sometimes give specific patterns of malformations. Infants with multiple malformations are therefore of a special interest. Two or more malformations in the same infant may have different causes.

Random hits are one explanation which may explain some infants with two malformations but very few infants with three or more malformations. If we suppose that 3 % of all infants have a major malformation, only one in 1100 will have two by the random occurrence of two different malformations and only about 1 in 37,000 will have three. The actual rates of infants with two or three different malformations are much higher.

Another explanation to the presence of two malformation codes for the same infant is the phenomenon of *sequences.* This means that one malformation is a

direct result of another, the primary one. Classical examples are that infants with spina bifida often have hydrocephaly or pes equinovarus as a result of the spinal cord malformation. Another example is pulmonary hypoplasia and facial dysmorphology as the result of absence of kidneys, Potter sequence. Infants with cardiovascular malformations often have more than one cardiovascular malformation code even though the primary damage to the heart rudiment probably is a single hit. Sequences should be regarded as single malformations, that is, as the primary anomalies which gave secondary changes.

A third group of multi-malformed infants are represented by *syndromes*. This term is often misused but should refer to defined constellations with a known cause. Examples are the rubella syndrome, with congenital cataract, hearing problems, and cardiovascular defects, and numerous genetic syndromes. If the cause is quite certain, such cases can be removed from the analysis but they are relatively few. At the detection of a new syndrome, often one leading malformation is first identified (in the case of the rubella syndrome, it was cataract and in the case of the thalidomide syndrome, it was amelia or phocomelia) and other characteristics are added later when groups of syndrome children are investigated.

The fourth group consists of constellations or patterns of malformations which are known but has no definite explanation, the *nonrandom association* of congenital malformations. Many such conditions are known; we can exemplify it with the VATER or VACTERL constellation which contains vertebrate, anal, trachea-esophageal, and radial or renal malformations (VATER), sometimes with cardiac malformations added (VACTERL). This is not a very unusual type of multi-malformed infant and may form an entity without known cause; it can be regarded as a syndrome looking for its cause! The explanation to a nonrandom association may be similarities in the embryogenesis and/or timing of the various malformations and may therefore not suggest a common cause like a drug exposure.

Finally we have the large group of multi-malformed infants which do not fit into any of the abovementioned groups. They may turn up to be unidentified syndromes or at least nonrandom associations when enough data have been collected. This group of infants is of great interest in a search for teratogenic drugs and should preferably be described in detail in the reports.

6.4 Causes of Congenital Malformations

6.4.1 Genetics

Some congenital malformations are monogenic conditions. Examples are achondroplasia which is usually a dominant mutation, some forms of microcephaly which are autosomal recessive, and some forms of hydrocephaly which are X-bound recessives. For these conditions, exposures during pregnancy are of little interest and such cases could be left out from analysis, but they are few. One also has to consider the possibility that the drug (if used before conception) could

cause a dominant mutation in the egg or sperm, resulting in a malformation. There is also a possibility that the drug causes a phenocopy, a condition which looks like a genetic condition. A classic example is warfarin which may cause a skeletal anomaly which resembles a genetic condition, chondrodystrophia calcificans. The constellation of malformations caused by mycophenolate mofetil (see p. 10) could be taken for the CHARGE association, a chromosome 18q deletion, or the HMC (hypertelorism-microtia-clefting) syndrome (Perez-Atyes et al. 2008). I think there is no reason to remove the very few cases of monogenic conditions which may turn up in an analysis. They may dilute the results but the effect will be small.

Many malformations have a genetic component which is more complex. So, for instance, orofacial clefts often occur in more than one family member, men with hypospadias have an increased risk to father a boy with this malformation, and couples who have had one fetus with spina bifida has a markedly increased risk to have another. Some investigators prefer to remove cases with a known family history of the malformation from the analysis, others do not. If the genetic trait is strong, such cases will dilute the material. On the other hand, it is possible that the genetic background makes the embryo especially sensitive for an environmental factor, for instance, maternal drug use. My preference is to keep cases with a family history; they might bias the risk estimate slightly toward null but this is not certain. If data are available, it is of course of interest to compare cases with and without a family history of the malformation, but it is rare that large enough numbers are present to allow such comparisons.

6.4.2 Chromosome Anomalies

A similar situation as with monogenic conditions exists for chromosome anomalies. The chromosome anomaly may be inherited from one of the parents or have occurred at the meiotic divisions at the formation of the egg or sperm. Many chromosome anomalies result in congenital malformations. If we take the most common autosomal anomaly, trisomy 21, it causes Down syndrome with typical dysmorphology and mental retardation but also with an increased risk for structural congenital malformations – heart defects – may occur in 40–50 % of these children and also other malformations occur in excess, e.g., duodenal atresia.

A difference between monogenic conditions and chromosome anomaly is that the latter are relatively common, even though modern prenatal diagnosis to some extent prevents the birth of such infants. The diagnosis is usually also definite after karyotyping. In analyses of specific malformations, infants with chromosome anomalies are usually excluded because the effect of the chromosome anomaly is such a strong cause of the malformation. There is, however, an interesting question – resembling the situation at familial malformations – that embryos carrying the chromosome anomaly could be more sensitive for external influences than normal embryos. Some studies have been made on Down syndrome to test this hypothesis but with no clear-cut results.

Chromosome anomalies should be included in the group "major malformations," but in the analysis of specific malformations, they should be left out (or treated as a separate group).

6.4.3 External Factors

Maternal use of drugs as a teratogenic factor is the main theme of the present book. Other external factors may disturb embryonic development with malformations as a result. If they somehow are associated with drug use, they may appear as confounders as will be discussed later. It is also possible that such factors may act synergistically with the drug.

Among such external factors can be mentioned some virus infections (notably rubella), strong ionizing irradiation, alcoholism, smoking, and some occupational exposures (Fixler and Threldkeld 1998). Some of them will be discussed in Chap. 8 on confounding. Other external factors are more uncertain like hot baths, showers or sauna, and nutritional deficits, and an association with specific drug use is also less likely.

6.5 Sources of Information on Malformations

In small studies information on malformations can be obtained by scrutiny of medical records from various disciplines. Sometimes interview or questionnaire information is obtained from parents or general practitioners who may be uncertain sources. For large-scale investigations one usually has to use register data.

There are different types of registers which can help to identify infants with malformations. There are specific malformation-monitoring registers around the world of varying quality and content. There are also international organizations which collect data from the various registers, e.g., the International Clearinghouse for Birth Defects Surveillance and Research and the European EUROCAT. Also within the USA, collaboration between different state registers occurs. An example is the National Birth Defects Prevention Study where data on some selected malformations are collected for epidemiological analysis from a number of state registers.

In the Scandinavian countries, medical birth registers exist which contain medical data on all pregnancies which end as deliveries. Late abortions are sometimes also included. Information on congenital malformations is incomplete when it is based on obstetric instead of pediatric information. In the Swedish register, infant information is given by qualified pediatricians who examine every infant born, but in spite of this, only a proportion of all malformations are identified. This information can be supplemented with discharge diagnoses from hospitalizations of the newborns and in some of the countries with data from specific registers of congenital malformation where reports are obtained from pediatricians and pediatric clinics. The linkage of the different sources of information is made with the use of the unique personal identification numbers of the mother and the infant. This system gives a relatively good ascertainment, but it is probably not complete. All internal

malformations are not detected in the newborn period, and follow-up is often only made during the first year of life when most but not all such conditions are identified.

The use of discharge diagnoses from neonatal units results in a complication. After some exposures, e.g., maternal use of antidepressants, neonatal morbidity increases and infants are often transferred to neonatal units, not because of a malformation but because of other morbidities. If no similar examination of non-transferred infants is made, a biased recording will be obtained. This may, for instance, explain the fact that most investigators find no effect on malformation rate after SSRI exposures (e.g., Källén et al. 2013), but in studies from Denmark (Pedersen et al 2009; Kornum et al. 2010; Jimenez-Solem et al. 2012), exclusively using discharge diagnoses from neonatal units, some malformation risks are seemingly increased.

Whichever technique for ascertainment is used, it is imperative that the same method is used for exposed and unexposed infants. If ascertainment is incomplete, it will reduce the power of the analysis but affect risk estimates only little as will be explained later in this book.

6.6 Prenatal Diagnosis and Induced Abortion

Today prenatal sonographic examination and other prenatal diagnostics are routine in developed countries. Then some malformed fetuses are identified and the woman can then choose to have her pregnancy interrupted with an induced abortion. The level of prenatal malformation detection depends on the equipment and the qualification of the investigator. In most but not all countries, there is an upper gestational age limit after which an abortion is not allowed. Detection of malformations at a second ultrasound around week 32 may then not result in an abortion. Late pregnancy detection, for instance of hydronephrosis, can increase the rate of registration after birth.

In some populations (e.g., Denmark, Finland) it is possible to link information on aborted fetuses with maternal drug use, in others (e.g., Sweden) law prohibits the registration of abortions with identification numbers and no linkage can be made.

Most malformations which are detected early enough to permit an abortion are relatively severe. A large proportion consists of chromosomally abnormal fetuses (which are of relatively little interest in studies of drug effects). Another large group is anencephaly and related malformations which are easily detected and nearly always aborted. This will result in the birth of only very few infants with anencephaly, and if analyses are restricted to infants born, an association between maternal drug use and anencephaly is difficult to detect. Other severe malformations are sometimes but not always detected and the fetus aborted. If aborted fetuses with spina bifida are not taken into consideration, an association with drug use can still be observed, but the study power will obviously be decreased. It can be illustrated with Swedish data on the association between maternal use of valproic acid and infant spina bifida. Among 5214 infants exposed in utero for anticonvulsants, 365

(7 %) were exposed to valproic acid. Four of the 5214 infants had spina bifida; all had been exposed to valproic acid. The expected number of spina bifida cases after valproic acid exposure is 0.28, and the observed number of four is significantly high (95 % Poisson confidence interval of 4 is 1.09–10.2). The risk estimate is a 14 times increase which agrees well with the 10–20 times risk increase stated in the literature. Prenatal diagnosis may have been intensified because of the valproic acid exposure which would have biased the risk estimate based on newborns toward null.

Another group of malformed infants which may be especially sensitive to prenatal diagnosis and may be a target for drug teratogenesis is multi-malformed infants. For this group a problem exists: aborted fetuses may be registered according to the malformation which was detected at the prenatal diagnosis, and other malformations present may not be recorded, notably if the aborted fetus was not autopsied by a fetal pathologist.

A study from Israel (Levy et al. 2012) claimed that exclusion of induced abortions biased the risk estimates toward null, illustrating it with data on folic acid antagonists. From the presented data, one can see that a majority of exposed neural tube defects in this population were detected and aborted (29 of 31), and this was true for about half of the cardiovascular defects (8 of 15). The corresponding percentages for unexposed cases were 15 % and 5 %, respectively. Thus the fact that women had used these drugs resulted in a considerable increase in induced abortions (as a result of intensified prenatal investigations) which made it nearly impossible to detect an effect on infants born, notably on neural tube defects. If this diagnostic increase was the same for well-known teratogens like anticonvulsants and notably valproic acid and for less known drugs is not clear from the study.

6.7 Grouping of Congenital Malformations

The concept of congenital malformations covers a large number of different conditions with different embryology. It is possible but unlikely that a teratogenic factor causes all types of malformations. There is a reason to divide the malformations into smaller and more homogeneous groups. This does not mean that the risk for any (major) malformation is uninteresting; this is actually the risk which the pregnant woman is mainly interested in.

There is no standard way to divide malformations into subgroups. The chapter division of the ICD code is often followed, but this is really not a good idea. The ICD codes were arranged in a way to make it easy to find a specific malformation and are therefore based on organ systems (with some exclusion like chromosomal anomalies or malformation syndromes). Each such group may consist of very different malformations with different embryogenesis. This will result in a grouping of malformations of different nature or to a spreading of related malformations to different groups.

Musculoskeletal malformations contain, for example, as different malformations as pes equinovarus and other positional foot defects, limb reduction defects, achondroplasia, and body wall defects. Even a subgroup of “body wall defects” contains

Table 6.1 Suggested grouping of congenital malformations among 5214 infants exposed to anticonvulsants in early pregnancy

Malformation	Number	Comment
Any malformation	365	
Relatively severe malformations	244	
Down syndrome	5	
Other chromosome anomalies	3	2 Turner syndrome
Neural tube defects	4	1 encephalocele, 3 spina bifida
Brain malformations	10	4 midline defects
Eye malformations	5	Different types
Orofacial clefts	19	12 cleft palate, 7 cleft lip/palate
Cardiovascular defects	92	51 only ventricular and/or atrium septum defect
Alimentary tract atresia	7	2 esophageal, 3 small gut, 2 anal atresia
Major kidney malformations	4	3 agenesis/hypoplasia, 1 cystic kidney
Hydronephrosis or urinary tract obstruction	12	9 hydronephrosis, 1 ureter obstruction, 2 vesico-ureter-renal reflux
Hypospadias	44	
Diaphragmatic hernia	4	
Body wall defects	2	1 omphalocele, 1 gastroschisis
Craniostenosis	5	
Poly- or syndactyly	18	11 polydactyly, 7 syndactyly
Limb reduction defects	3	1 cleft hand/foot, 1 absent leg, 1 longitudinal arm defect
"Syndromes"	2	1 probable Pierre-Robin sequence

very different malformations: omphalocele, gastroschisis, and large body wall defects, with different embryogenesis and epidemiological characteristics. Also limb reduction defects consist of different subgroups with different characteristics like transverse and longitudinal reduction defects.

Urogenital malformations contain very different types, for instance, absence of kidney or renal dysplasia, obstructive malformations leading to hydronephrosis, and hypospadias.

On the other hand, esophageal atresia, small gut atresia, and anal atresia show many similarities in embryogenesis and epidemiology but belong to different groups: Q39, Q41, and Q42.

Table 6.1 gives an example how an embryological more reasonable summary of a group of observed malformations can be given. It summarizes relatively severe malformations among 5214 Swedish infants exposed to anticonvulsants in early pregnancy, tentatively grouped according to embryological principles. Note that some infants had more than one malformation.

Ten of these infants had combinations of major malformations; five of them had hypospadias.

These cases should also be listed:

Malformations
Cleft palate + hypospadias + ASD + tongue malformation
Cleft lip/palate + hypospadias + VSD/ASD/CoA + syndactyly
Hypospadias + ASD
Hypospadias + VSD
Hypospadias + pes equinovarus
VSD/ASD + split hand and foot
VSD + polydactyly
Subaortic stenosis + bile duct atresia
Unspecified brain malformation + VSD
Malformation of anterior eye segment + ASD

ASD atrium septum defect, *CoA* coarctation of aorta, *VSD* ventricular septum defect

This type of reporting of malformations also makes it possible to add detailed materials from different investigations.

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