Guidelines

Guidelines for Case Classification for the National Birth Defects Prevention Study

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BACKGROUND: Previous studies have suggested that etiologic heterogeneity may complicate epidemiologic analyses designed to identify risk factors for birth defects. Case classification uses knowledge of embryologic and pathogenetic mechanisms to make case groups more homogeneous and is important to the success of birth defects studies. **METHODS:** The goal of the National Birth Defects Prevention Study (NBDPS), an ongoing multi-site case–control study, is to identify environmental and genetic risk factors for birth defects. Information on environmental risk factors is collected through an hour-long maternal interview, and DNA is collected from the infant and both parents for evaluation of genetic risk factors. Clinical data on infants are reviewed by clinical geneticists to ensure they meet the detailed case definitions developed specifically for the study. To standardize the methods of case classification for the study, an algorithm has been developed to guide NBDPS clinical geneticists in this process. **RESULTS:** Methods for case classification into isolated, multiple, and syndrome categories are described. Defects considered minor for the purposes of case classification are defined. Differences in the approach to case classification for studies of specific defects and of specific exposures are noted. **CONCLUSIONS:** The case classification schema developed for the NBDPS may be of value to other clinicians working on epidemiologic studies of birth defects etiology. Consideration of these guidelines will lead to more comparable case groups, an important element of careful studies aimed at identifying risk factors for birth defects. *Birth Defects Research (Part A) 67:193–201, 2003.* © 2003 Wiley-Liss, Inc.

INTRODUCTION

Birth defects are a leading cause of infant mortality in the United States (Hoyert et al., 2001), yet the causes of most birth defects are unknown (Nelson and Holmes, 1989). The National Birth Defects Prevention Study (NBDPS) is a large, ongoing case–control study, sponsored by the Centers for Disease Control and Prevention (CDC) and designed to identify genetic and environmental factors important in the etiology of birth defects (Yoon et al., 2001). This study, based in eight birth defects surveillance systems located in Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, and metropolitan Atlanta, Georgia (CDC), includes collection of data on many potential exposures through maternal interview and collection of biological specimens for study of possible genetic susceptibility and gene–environment interaction. Infants with over 30 types of major congenital defects are included in the study (Table 1). Since the commencement of the study in October 1997, each site has contributed approximately 300 cases and 100 controls to the study per year. As of August 15, 2002, 12,190 cases and 5034 controls have been entered into the study. Clinical information on each infant, including all major and minor defects (both verbatim and coded diagnoses), methods of diagnosis, laboratory results, and relevant exposures or family history, as well as the study clinical geneticist's assessment of whether these findings represent a recognized pattern of malformation, is entered into a centralized clinical database.

The etiologic heterogeneity of birth defects has long been recognized (Holmes et al., 1976; Khoury et al., 1982; Martin et al., 1983; Murray et al., 1985; Jones, 1988; Cunniff et al., 1990; Ferencz, 1993). A single defect type, such as spina bifida, may be caused by a chromosome abnormality, a single-gene condition, or a teratogenic exposure, or may be of unknown cause. Etiologic heterogeneity may complicate epidemiologic studies designed to identify causes of birth defects (Friedman, 1992; Khoury et al., 1992a,b). Isolated birth defects have been shown to be epidemiologically and most likely etiologically distinct from defects associated

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Table 1
Birth Defects Eligible for Inclusion in the National Birth Defects Prevention Study

Birth defect
Anencephaly, craniorachischisis
Spina bifida
Encephalocele, cranial meningocele, encephalomyelocele
Holoprosencephaly
Hydrocephalus
Dandy-Walker malformation
Anophthalmia, microphthalmia
Cataracts, glaucoma and related eye defects[a]
Anotia, microtia
Conotruncal heart defects
Single ventricle
Septal heart defects (atrial septal defects, ventricular septal defects)
Atrioventricular septal heart defects
Ebstein malformation
Obstructive heart defects (right and left ventricular outflow tract defects)
Anomalous pulmonary venous return
Heterotaxia
Choanal atresia
Cleft lip +/− palate
Cleft palate
Esophageal atresia +/− tracheoesophageal fistula
Intestinal atresia/stenosis
Biliary atresia
Hypospadias, second or third degree
Renal agenesis/hypoplasia
Exstrophy, bladder
Exstrophy, cloacal
Limb deficiency, intercalary
Limb deficiency, longitudinal
Limb deficiency, transverse
Limb deficiency, not elsewhere classified
Craniosynostosis
Diaphragmatic hernia
Sacral agenesis
Omphalocele
Gastroschisis
Amnion rupture sequence

[a]Included in the study as of January 1, 2000.

with additional major defects. For example, isolated neural tube defects were more often observed in females and Caucasians, but these associations were not seen for neural tube defects associated with other major defects (Khoury et al., 1982). In addition, different risk factor associations have been noted in isolated and multiple cases (Khoury et al., 1989). For example, a protective effect of periconceptional multivitamin use was found for isolated conotruncal heart defects, but not for those associated with other noncardiac defects or with a recognized syndrome (Botto et al., 1996). Inclusion of infants with different causes in the study of a birth defect may dilute the magnitude of an observed association toward the null (Khoury et al., 1992a). Thus, the process of case classification is important to the success of epidemiologic studies of birth defects.

The goal of case classification is to use knowledge of embryologic and pathogenetic mechanisms to make case groups used for analysis more comparable (Khoury et al., 1994a; Martinez-Frias et al., 1990, 1991, 2000). In some studies, infants with the same defect will be classified for analysis into separate groups, based on whether the defect is isolated, one of multiple congenital anomalies, or associated with a syndrome, to make them presumably more homogeneous. In other studies, case classification may allow for infants with anatomically different, but presumed pathogenetically similar, defects to be combined to increase the power of a study. An example of this is combining infants with defects of presumed vascular etiology for study (Martin et al., 1992; Van Allen, 1992). NBDPS clinical geneticists have developed a system of terminology and case classification guidelines, adapted from the work of others (Spranger et al., 1982; Khoury et al., 1994a; Jones, 1997), to standardize the methods of case classification for the study. It should be acknowledged that some of the decisions made in developing these case classification guidelines were arbitrary; however, we believe that it is important that methods of case classification be as well-defined as possible, so that the process is uniform among different clinical geneticists. It is inevitable that some may wish to classify cases differently; we believe this is appropriate as long as details on how the case classification was done are provided and the process is consistent within the particular study. We are hopeful that the approach delineated here may be helpful to other clinicians involved in case classification for epidemiologic studies of birth defects.

CLASSIFICATION FOR STUDIES OF SPECIFIC DEFECTS

In the epidemiologic study of specific birth defects for possible risk factors, classification of infants involves two issues: 1) Does the infant have the defect of interest as an isolated defect, as one of multiple congenital anomalies, or as a component of a syndrome? We use the term "syndrome" here to refer to a recognizable pattern of multiple malformation that is known or presumed to have a specific cause (e.g., a single-gene condition, chromosome abnormality, or teratogenic exposure) (Khoury et al., 1994b); and 2) based on what is known about the pathogenesis of the defect of interest, is further classification warranted?

Given the complexity of the process of determining whether an infant has the defect of interest as an isolated defect, as one of multiple congenital anomalies or as a component of a syndrome, a stepwise approach may be advantageous and is summarized in Figure 1. This process requires that the reviewer have specific training in a mechanistic approach to birth defects and be familiar and up-to-date with the birth defects, genetics and dysmorphology literature; thus, we suggest that case classification is best carried out by a clinical geneticist/dysmorphologist when possible. If unavailable, a clinician with experience in birth defects and the availability of a clinical geneticist/dysmorphologist for consultation on complicated cases, especially those with multiple defects, will be adequate for analyses of certain defects.

Does the Infant Have at Least One Defect that Meets Case Definition Criteria for the NBDPS?

To maximize the usefulness of the data, case definitions have been standardized for the study, and clinical information on each infant is evaluated by a clinical geneticist located at each site before inclusion in the study. These case definitions include information on eligibility criteria (e.g., infants must have Type II , III, or IV microtia [Meur-

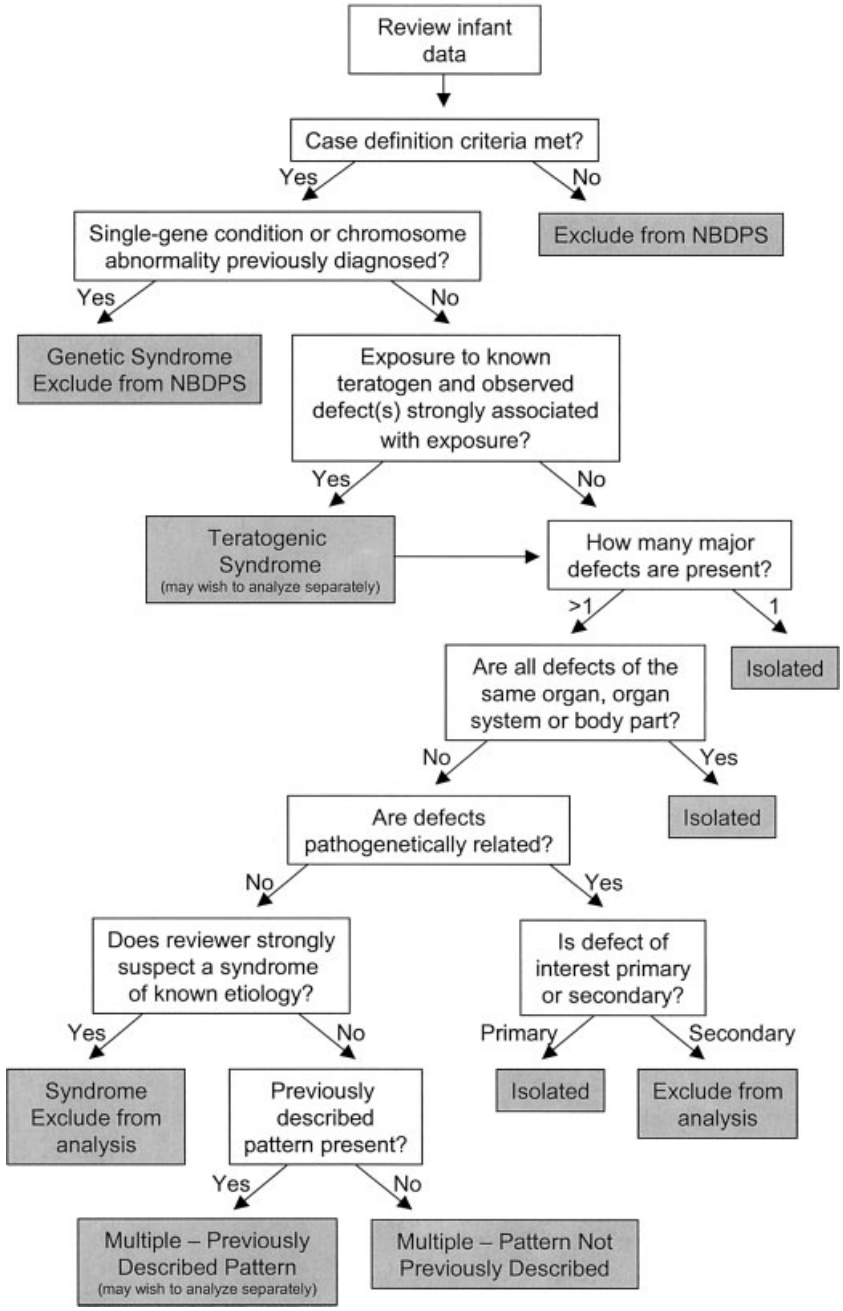

Figure 1. A summary of the process of determining whether an infant has the defect of interest as an isolated defect, as one of multiple congenital anomalies, or as component of a syndrome. Please refer to text for details on decision points.

man, 1957] to be included in the study as having anotia/microtia), methods of diagnosis (e.g., cardiac defects must be diagnosed by echocardiography, catheterization, surgery, or autopsy to be included in the study), and essential clinical information to be abstracted verbatim from medical records (e.g., information on other birth defects that frequently accompany the birth defect of interest). Although the specific case definitions developed for the NBDPS may not be appropriate for other birth defects studies, the importance of a careful, well-characterized case definition to studies of birth defects should be emphasized.

Has a Single-Gene Condition or Chromosome Abnormality Been Diagnosed?

Because the focus of the NBDPS is on cases of unknown etiology, infants with genetic syndromes (single-gene conditions or chromosome abnormalities) are excluded from the study. In the case of chromosome abnormalities, results of chromosome analysis (karyotype or fluorescence in situ hybridization [FISH] analysis) to support the diagnosis must be available. For single-gene conditions, only infants with single-gene conditions documented in the medical record are excluded. The clinical reviewer must determine

if the stated diagnosis is consistent with the defects described and was made by a qualified professional, based on the medical record data available. These genetic syndromes must be related to the defect, as opposed to being "additive." A defect can be described as additive to a syndrome if the defect has not been described previously in association with the syndrome, and has no known or plausible connection with the phenotype (e.g., galactosemia with limb deficiency).

Is an Exposure to a Known Teratogen Present and Is/Are Observed Defect(s) Strongly Associated with this Exposure?

Infants with defects believed to be related to a teratogenic exposure (e.g., sacral agenesis in a baby whose mother had diabetes mellitus) are included in the NBDPS. One reason for including these infants is that they offer an opportunity to study genetic factors that may contribute to the observed outcome (Buehler et al., 1994). In some analyses, an infant with defects that are associated strongly with a specific teratogenic exposure (e.g., an infant with anotia or microtia with maternal retinoic acid [Accutane] exposure) (Lammer et al., 1985) could be classified as having a teratogenic syndrome and excluded from specific investigations, depending on the analysis being carried out. We recommend that infants with defects that have a weaker association with a specific exposure (e.g., an infant with cleft lip with maternal phenobarbital exposure) (Arpino et al., 2000) not be excluded. Instead, they should be classified as having isolated or multiple defects, depending on additional defects present in that infant.

How Many Major Defects Are Present?

Several types of cases should be classified as "isolated." Infants who have only a single major defect should be classified as having an isolated defect; however, the converse is not true. Classification of an infant with more than one major defect must be based on information of known embryologic and pathogenetic mechanisms. Infants that should be classified as having an isolated defect include those with a single major defect with additional minor defects in the absence of a defined syndrome; with a major defect accompanied by other major defects in the same organ, organ system or body part; and with a major defect accompanied by other pathogenetically related defects (Table 2) (Khoury et al., 1994a).

Most epidemiologic studies of birth defects have concentrated on major defects, that is, those that have surgical, medical, or serious cosmetic importance. One reason for this is that ascertainment of minor anomalies has not been standardized (Lechat and Dolk, 1993) for birth defects surveillance programs that focus on abstraction of inpatient records. Minor defects are known to be important in the study of birth defects, however, because they often may accompany, and serve as an indication of, a syndrome of known etiology (Frias and Carey, 1996). In addition, the presence of three or more minor anomalies has been shown predictive of the presence of major malformations (Leppig et al., 1987). Because of their frequent occurrence in babies with major defects, we classify infants with a single major defect accompanied by any number of minor defects as having an isolated defect, assuming that a recognized syndrome is not present.

Table 2
Examples of Case Classification

Example	Case classification
Isolated diaphragmatic hernia, no other major or minor defects	Isolated (isolated major defect)
Cleft lip, left ear pit, mild hydronephrosis	Isolated (one major defect + two minors)
Tetralogy of Fallot, atrial septal defect	Isolated (two defects involving the same organ system)
Spina bifida, talipes equinovarus, hip dislocation, hydrocephalus	Isolated (several defects constituting a sequence [spina bifida is primary defect]--infant should be excluded from studies of other defects)
Cleft lip, transposition of great vessels	Multiple (two major, unrelated, specific defects)
Esophageal atresia with tracheoesophageal fistula, hemivertebrae, imperforate anus	Multiple (three major defects consistent with VACTERL association; may wish to analyze separately from other multiple cases)
Holoprosencephaly associated with Trisomy 13	Syndrome (chromosome abnormality)
Interrupted aortic arch associated with 22q11.2 deletion	Syndrome (chromosome abnormality)
Cleft palate associated with Stickler syndrome	Syndrome (autosomal dominant)

To define minor defects for NBDPS case classification purposes, lists of minor defects collected from previous sources (Marden et al., 1964; Hook et al., 1976; Leppig et al., 1987; Cohen, 1997; Chambers et al., 2001) were reviewed. Table 3 delineates the minor defects agreed upon by NBDPS clinical geneticists. Although an attempt has been made to make this list as complete as possible, clinical judgment will be necessary for its use. This list is also somewhat arbitrary, because some of the defects included as minor may, at times, be of surgical, medical, or serious cosmetic importance, or may be believed to be mild manifestations of a major defect (e.g., cleft uvula and cleft palate) (Frias and Carey, 1996). It is important, however, to designate a standard group of minor defects for an epidemiologic study; deviations from this list are acceptable but should be noted.

Are All Major Defects of the Same Organ, Organ System or Body Part?

Often, a major defect is accompanied by other related major defects. In some infants, these defects affect the same organ, organ system, or body part. Some examples include syndactyly and split hand deficiency of the same limb, multiple cardiac defects, esophageal atresia and tracheoesophageal fistula, and multiple neural tube defects, with other examples listed elsewhere (Khoury et al., 1994a). Because these defects are believed to be embryologically and pathogenetically related, we classify infants with these defects as having an isolated defect.

Are All Major Defects Related Pathogenetically?

Sometimes a major defect is accompanied by other major defects of a different organ, organ system, or body part,

but the pattern of structural defects can be attributed to a primary problem in morphogenesis that leads to a cascade of consequent defects. This pattern of defects is termed a "sequence" (Spranger et al., 1982; Jones, 1997). In many instances, the occurrence of one defect is thought to precede and directly influence the occurrence of one or more additional defects. Examples include spina bifida leading to the sequence defects talipes, hydrocephalus and axial skeleton malformations, and severe micrognathia leading to the sequence defects glossoptosis and cleft palate. In other instances, the error in morphogenesis seems to have been earlier, involving cells or tissues that will ultimately form more than one, often contiguous, body structure. Examples include hemifacial microsomia with defects of ear, jaw, and oral structures, and holoprosencephaly with defects of the brain, midface, and oral structures. In both of these situations, we classify infants with these combinations of defects as having an isolated defect because there is one "primary" defect (primary refers to the earliest defect in morphogenesis) (Jones, 1997).

Is the Defect of Interest Primary or Secondary?

Another important issue raised by these situations is identification of the group in which the defect should be analyzed. Clinical information should be evaluated to determine if the defect under study is primary, or whether the defect of interest is presumed to be secondary to another defect. For example, infants with meningomyelocele often also have clubfoot secondary to the neural deficit related to the lesion (Jones, 1997). We believe these infants would be more appropriately analyzed for etiologic risk factors with other infants with meningomyelocele, rather than with infants with clubfoot, because the clubfoot is believed to be secondary to the meningomyelocele. Sometimes, the selection of an appropriate analysis group is more apparent (e.g., an infant with holoprosencephaly and midline cleft lip should be analyzed with other infants with holoprosencephaly, and not with infants with cleft lip), but other times determining the appropriate analysis group can be challenging. For example, the appropriate analysis group for an infant with hemifacial microsomia consisting of microtia, mandibular hypoplasia, and cleft lip and palate is not as clear. These infants may be excluded from the analysis or analyzed separately, if sufficient numbers of infants with these phenotypes are available.

We suggest that sequence designation should be limited to those defects that occur as a consistent, frequent finding with the primary defect (e.g., spina bifida and clubfoot). In some instances, a sequence may be suspected, but the finding is not consistent or frequent and could represent unrelated malformations. For example, in an infant with a large omphalocele and clubfeet, one could postulate that the clubfeet are part of a sequence, related to constricted movement as the result of the space-occupying lesion. Because clubfeet rarely accompany omphalocele, however, the clinical geneticist should not presume that this is a sequence; instead, the infant should be classified as having multiple defects.

In considering an infant as having an isolated defect, it should be noted that the defects identified in a child may be time-dependent, because some defects may not be recognized until later in life or may be dependent on additional studies, such as echocardiography or brain imaging studies. For example, brain abnormalities have been identified by MRI in individuals presumed to have isolated, nonsyndromic cleft lip or palate (Nopoulos et al., 2001, 2002).

When a defect of interest is accompanied by at least one additional unrelated, major and specified defect and the etiology of the defects is unknown, we recommend that the infant should be classified as having multiple defects (Khoury et al., 1994a) (Table 2). The term "unrelated" refers to defects in different body parts or systems and not part of a sequence, as discussed previously. The term "major" refers to the exclusion of minor defects, discussed above and listed in Table 3. The defect also must be "specified" or adequately described. This excludes defects that are not well-delineated (e.g., ear defect, malformed limbs) and often coded as "not otherwise specified" (NOS). Infants with genetic syndromes of known etiology should be excluded from this group (see below).

Does the Reviewer Strongly Suspect a Genetic Syndrome of Known Etiology?

Infants in whom a chromosome abnormality or single-gene disorder is suspected by the study clinical geneticist, but not identified by clinicians who examined the infant, have been included in the study. Depending on the analytic study planned, these infants may be excluded by the clinical geneticist involved in an analysis. For example, a stillborn infant with holoprosencephaly and polydactyly in whom chromosome analysis was not carried out may be excluded from a study of risk factors of holoprosencephaly, given the suspicion that the infant may have Trisomy 13 or Pseudotrisomy 13 (postulated to be autosomal recessive) (Lurie and Wulfsberg, 1993). Exclusions such as these, however, should be specifically noted in the study methods.

A syndrome classification might also be considered in the absence of a definitive diagnosis in the case of a positive family history. Because the etiology of most isolated birth defects is believed to be multifactorial, increased risk among relatives is expected, but the magnitude of recurrence risk does not approach that of a single-gene disorder. For some defects, however, the relative contribution of single-gene disorders may be notably higher. For example, congenital cataracts are often inherited in an autosomal dominant manner (Francis et al., 2000); thus, an infant with congenital cataracts whose parent also had congenital cataracts could be classified as having a syndrome (presumed autosomal dominant single-gene condition), even if the particular single-gene condition had not been identified. In contrast, a family in which both a child and his parent have a cleft lip (not an infrequent occurrence) would not be classified as having a syndrome because the relative contribution of single-gene disorders to clefting is low. Several issues should be taken into account when considering a positive family history, including whether the family history is consistent with a specific type of inheritance (e.g., autosomal dominant), the degree of relationship between the proband and the affected family members, and the relative contribution of single-gene disorders to the defect. Positive family history does not necessarily imply genetic etiology. Other causes of a positive family history include shared environmental exposure and, for common defects, coincidence in large families. Information about how infants with positive family history were classified should be provided in the study methods. Improved understanding

Table 3
Defects Considered to be Minor, Prematurity-Related, or Nonstructural for Case Classification Purposes of the National Birth Defects Prevention Study

Anomaly	Case*
Congenital anomalies of the brain and nervous system	
Absent septum pellucidum	742.280
Hydrocephalus secondary to intraventricular hemorrhage (IVH)	742.385
Macrocephaly	742.400
Congenital anomalies of the eye	
Iris coloboma	743.430
Iris freckles	743.440
Blue sclera	743.450
Ptosis	743.600
Absence of eyelashes	743.630
Long eyelashes	743.630
Weakness of eyelids	743.630
Fused eyelids	743.630
Short palpebral fissures	743.635
Stenosis or stricture of lacrimal duct	743.650
Exophthalmos	743.800
Epicanthal folds	743.800
Epicanthus inversus	743.800
Upward or downward slanting palpebral fissures	743.800
Brushfield spots	743.800
Epibulbar dermoid cyst	743.810
Congenital anomalies of the ear, face, and neck	
Preauricular appendage, tag, or lobule	744.110
Ear tag	744.120
Large ears	744.200
Misshapen ears	744.220, 744.280
Crumpled ears	744.230
Protruding ears	744.230
Small ears (excludes true microtia)	744.230
Lack of helical fold	744.230
Thickened or overfolded helix	744.230
Absent tragus	744.230
Asymmetric sized ears	744.230
Darwinian tubercle	744.230
Double lobule	744.230
Bridged concha	744.230
Ear lobe crease	744.230
Low-set ears	744.245
Posteriorly rotated ears	744.246
Narrow external auditory meatus	744.280
Ear pit	744.410
Webbed neck	744.500
Redundant neck folds	744.500
Large, wide lips	744.820
Small lips	744.830
Short neck	744.900
Congenital anomaly of face, not otherwise specified (NOS); abnormal facies	744.910
Bulbus cordis anomalies and anomalies of cardiac septal closure	
Patent foramen ovale	745.500
Other congenital anomalies of the heart	
Pulmonary valve insufficiency	746.020
Thickened pulmonary valve	746.080
Tricuspid valve insufficiency	746.105
Aortic valve insufficiency	746.400
Bicuspid aortic valve	746.400
Thickened aortic valve	746.480
Mitral valve insufficiency	746.600
Dextrocardia without congenital heart defects	746.800
Anomalies of myocardium	746.860
Ventricular hypertrophy (right or left)	746.886
Thickened cardiac valve	746.900
Heart murmur	746.990
Other congenital anomalies of the circulatory system	
Patent ductus arteriosus	747.000
Peripheral pulmonic stenosis (PPS)	747.325
Single umbilical artery	747.500
Congenital anomalies of the respiratory system	
Small nares	748.180
Anteverted nares	748.180
Notched or hypoplastic alae nasi	748.180
Flat or wide nasal bridge	748.180
Congenital laryngeal stridor	748.360
Hypoplasia of lung (in premature infants)	748.510
Cleft palate and cleft lip	
Bifid uvula	749.080
Cleft gum	749.190
Other congenital anomalies of the upper alimentary tract	
Tongue-tie	750.000
Microglossia	750.110
Macroglossia	750.120
Aberrant frenula	750.180
High arched palate	750.240
Angular lip pits	750.260
Short/long columella	750.270
Thin vermilion border	750.270
Smooth philtrum	750.270
Broad alveolar ridge	750.280
Pylorospasm	750.500
Other congenital anomalies of the digestive system	
Meckel diverticulum	751.010
Rectal fissure	751.580
Hepatomegaly	751.620
Congenital anomalies of the genital organs	
Imperforate hymen	752.430
Fusion of vulva	752.440
Prominent clitoris	752.450
Embryonal cyst of vagina	752.460
Cyst of vagina, vulva, or canal of Nuck	752.470
Vaginal or hymenal tags	752.480
Hypoplastic labia majora	752.480
Hypoplastic labia minora	752.480
Median raphe present (female)	752.480
Undescended testicles	752.500–752.520
First degree hypospadias +/− chordee	752.605, 752.625
Chordee	752.621
Hypoplasia of testis and scrotum	752.810
Shawl scrotum	752.820
Absent or hooded foreskin of penis	752.860
Redundant foreskin	752.860
Small penis (unless documented as micropenis)	752.865
Scrotalization of phallus	752.880
Absent median raphe (male)	752.880
Congenital anomalies of the urinary system	
Mild, minimal hydronephrosis	753.200
Ectopic kidney (unless documented as pelvic kidney)	753.330
Patent urachus	753.700
Urachal cyst	753.710
Certain congenital musculoskeletal deformities	
Facial asymmetry	754.000
Deviation of nasal septum	754.020
Dolichocephaly	754.030

[a]Refers to ICD-9-based six-digit coding scheme for birth defects developed by CDC from the BPA-modification of ICD-9 (Rasmussen and Moore, 2001). Not all defects included in these codes should be considered minor.

Table 3
Defects Considered to be Minor, Prematurity-Related, or Nonstructural for Case Classification Purposes of the National Birth Defects Prevention Study (continued)

Anomaly	Code*	Anomaly	Code*
Third fontanelle	754.040	Spina bifida occulta	756.100
Large or small fontanelles	754.040	Cervical rib	756.200
Metopic suture open to bregma	754.040	Diastasis recti	756.790
Plagiocephaly	754.050	Torticollis	756.860
Head asymmetry	754.055	Congenital anomalies of the integument	
Trigonocephaly, other head deformations without synostosis	754.070	Single transverse palmar crease	757.200
Hip click	754.310	Extra or absent hand/interphalangeal creases	757.200
Hip subluxation	754.310	Unusual dermatoglyphics	757.200
Genu recurvatum	754.430	Skin tag	757.310
Metatarsus varus or metatarsus adductus	754.520	Anal tag	757.310
Pectus carinatum	754.800	Nevus flammeus	757.380
Pectus excavatum	754.810	Port-wine stain	757.380
Deformed chest	754.820	Birthmark	757.385
Barrel chest	754.820	Mongolian spot	757.386
Bifid xiphoid	754.820	Depigmented or hyperpigmented spot	757.390
Shieldlike chest	754.825	Café-au-lait spot	757.390
Other congenital anomalies of limbs		Cutis marmorata	757.390
Postaxial minimus polydactyly in African-Americans	755.006	Skin cyst	757.390
Syndactyly (involving 2nd and 3rd toes)	755.130	Excessive or persistent lanugo	757.450
Broad, triphalangeal thumb	755.500	Aberrant scalp hair patterning	757.480
Tapered fingers	755.500	Hair upsweep	757.480
Overlapping fingers	755.500	Low posterior hairline	757.480
Short fingers	755.500	Depigmentary hair changes	757.480
Long fingers	755.500	Synophrys, confluent or medial flare eyebrows	757.480
Clinodactyly	755.500	Thickened toenails	757.510
Camptodactyly	755.500	Hyperconvex fingernails	757.580
Dimple—hand	755.510	Hyperconvex toenails	757.580
Short 4th metacarpal	755.510	Hypoplastic fingernails	757.585
Cubitus valgus	755.540	Hypoplastic toenails	757.585
Dimple shoulder	755.550	Absent nipple	757.630
Recessed 4th and 5th toes	755.600	Small nipple (hypoplastic)	757.640
Widely spaced 1st and 2nd toes	755.600	Accessory nipple	757.650
Overlapping toes	755.600	Widely spaced nipples	757.680
Short or broad great toe	755.600	Inverted nipples	757.680
Long toes	755.600	Other specified and unspecified congenital anomalies	
Hallux valgus	755.605	Splenomegaly	759.020
Hallux varus	755.606	Anomalies of thymus, thymic hypertrophy (absent thymus should be considered a major defect)	759.240
Short 4th metatarsus	755.610		
Plantar furrow	755.610	Anomalies of umbilicus, low-lying umbilicus	759.900
Sole crease	755.610		
Prominent heel	755.610	Other anomalies (not coded in congenital anomalies section)	
Rocker-bottom feet	755.616		
Tibial torsion	755.630	Benign skin neoplasm, pigmented nevus	216.000–216.900
Hyperextended knee	755.640		
Genu valgum	755.645	Noncavernous, single, small hemangioma (<4" diameter)	228.000; 228.010
Genu varum	755.646		
Anteversion of femur	755.650	Facial palsy	351.000
Coxa valga	755.660	Esotropia	368.000
Coxa vara	755.660	Exotropia	378.000
Hyperextended joints, NOS	755.880	Strabismus	378.900
Overlapping digits, NOS	755.880	Nystagmus	379.500
Other musculoskeletal anomalies		Natal teeth	520.600
Flat occiput	756.080	Micrognathia	524.000
Prominent occiput	756.080	Prognathia	524.000
Bony occipital spur	756.080	Inguinal hernia	550.000–550.900
Narrow bifrontal diameter	756.080	Umbilical hernia	553.100
Prominent or hypoplastic supraorbital ridges	756.080	Testicular torsion	608.200
		Pilonidal or sacral dimple	685.100
Frontal bossing	756.080	Erb's palsy	767.600
Minor hypotelorism	756.080	Meconium plug syndrome	777.100
Maxillary hypoplasia/prominence	756.080	Meconium peritonitis	777.600
Dystopia canthorum	756.085	Ascites, congenital	778.000
Minor hypertelorism	756.085	Hydrocele	778.600

of genes and their contribution to individual birth defects may assist in deciding which infants with a positive family history should be classified as having syndromes (Schott et al., 1998).

Is a Previously Described Pattern Present?

Some infants have a recognized phenotype, but of unknown etiology. In some cases, these constitute "associations", nonrandom occurrences of certain defects of unknown etiology, such as the VACTERL association (Khoury et al., 1983) or CHARGE association (Blake et al., 1998). Other infants with recognized phenotypes may have "recurrent pattern syndromes" (Cohen, 1997), defined as a similar set of anomalies in two or more unrelated patients of unknown etiology. Although these recognized phenotypes of unknown etiology are often referred to as syndromes, the use of this terminology has been questioned (Khoury et al., 1994b), given that their etiology remains unknown and may be heterogeneous (Khoury et al., 1983). Recognized phenotypes of unknown etiology should be noted by the clinical geneticist. Depending on the study, these infants may be analyzed separately from other infants classified as having multiple defects (Lammer et al., 1986).

Sometimes, based on what is known about the pathogenesis of the defect, further case classification may be appropriate. For example, because neural tube defects may be due to different embryologic mechanisms, depending on the level of the defect, classifying infants with neural tube defects based on the site of their lesion may be useful (Park et al., 1992). Another possible scenario is that individual defects that are believed to be embryologically or pathogenetically similar can be combined to maximize the number of cases analyzed. For example, grouping of congenital heart defects according to their presumed underlying pathogenetic mechanism (Clark, 1996) may be a reasonable approach to their study. A recent study of risk factors in different individual conotruncal defects showed little evidence of risk factor heterogeneity, providing support for analyzing these defects as a single category (O'Malley et al., 1996); however, other studies have shown more heterogeneity within this category (Ferencz et al., 1997).

It is important to recognize that improved understanding of the pathogenesis of birth defects may result in changes in case classification. This issue needs to be considered in the planning of epidemiologic studies of birth defects, because it is essential that clinical information continue to be available so that case classification can be modified as advances in the understanding of birth defects occur.

CLASSIFICATION FOR STUDIES OF SPECIFIC EXPOSURES

Case classification for studies of specific exposures (e.g., case–control study of maternal use of a specific prescription drug) differs somewhat from the approach to case classification for studies of specific defects (e.g., case–control study examining several risk factors for gastroschisis). The focus of case classification, however, continues to be on what is known about embryogenesis and pathogenesis of the defects and on the exposure of interest. Special interest may be given to infants with multiple defects, because many human teratogens have been recognized because of similar patterns of multiple congenital anomalies (Friedman, 1992). The clinical geneticist should scrutinize infants with multiple congenital anomalies for possible new patterns of malformation that may be associated with the exposure. In addition to the use of the clinical geneticist's expertise to recognize new phenotypes, statistical associations may also be explored using defined methods (Kallen et al., 1999).

If information is available on the potential action of the exposure of interest, this can be applied to case classification. As an example, cocaine exposure has been hypothesized to be associated with vascular disruptive defects (Hoyme et al., 1990); therefore, lumping of defects believed to be secondary to vascular disruption (gastroschisis, transverse limb deficiency, and small intestinal atresia) may be appropriate in a study of cocaine teratogenesis (Khoury et al., 1992b; Martin et al., 1992).

An issue separate from case classification, but related and important to studies of specific exposures, is whether the defects observed are consistent with the known timing of the exposure. For example, transposition of the great arteries could not have been caused by a third-trimester exposure, and limb deficiency and ring constriction of digits related to amniotic band sequence is unlikely to be due to a periconceptional exposure. The pathogenesis of the defect (malformation, deformation, disruption, or dysplasia) also needs to be assessed in light of what is known about the action of the exposure. Information about the pathogenesis of the defects observed and the timing of exposure reported needs to be consistent for an association to be plausible. These are all areas where the contribution of the clinical geneticist to the study of exposure is critical.

We have summarized here the guidelines for case classification in birth defects epidemiology used by the NBDPS. We believe adoption of these guidelines will lead to more comparable and etiologically homogeneous case groups for the study of birth defects, an important element of careful studies aimed at identifying risk factors for birth defects. To ensure that NBDPS clinical reviewers consistently review and classify cases, inter-reviewer reliability studies are carried out periodically. Sufficient numbers of cases with specific defect types have become available in the NBDPS only recently; thus, evidence of the utility of the case classification process in the NBDPS remains to be demonstrated. Previous studies have shown, however, that the case classification process can help to define risk factors that might otherwise be missed (Khoury et al., 1989; Botto et al., 1996). Other clinicians may find consideration of these guidelines beneficial in their work on epidemiological studies of birth defects.

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