Inclusion and Exclusion Criteria for Malformations in Newborn Infants Exposed to Potential Teratogens

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BACKGROUND: The surveillance of newborn infants exposed to potential teratogens often relies on the findings in routine physicians' examinations to identify malformations. Exposed newborn infants can have a wide variety of physical features, including malformations, birth marks, positional deformities, and minor anomalies. The routine physician's findings are not standardized. Some physicians record a wide variety of physical features and others do not. The purpose of this study was to develop criteria and definitions for identifying malformations and for identifying the more common and less severe physical features that would be excluded as not being malformations. **METHODS:** The physical features recorded by the examining pediatricians were obtained from a review of the medical records of a consecutive sample of 1000 liveborn and stillborn infants and elective terminations for fetal anomalies. **RESULTS:** A malformation, defined as a structural abnormality with surgical, medical or cosmetic importance, was present in 18 (2.8%) of the infants; 222 other recorded features were identified and excluded: malformations attributed to dominant or recessive genes (4) or chromosome abnormalities (6), minor anomalies and normal variations (65), birth marks (110), positional deformities (6), prematurity-related features (5), physiologic findings (4) and findings identified by prenatal ultrasound (but not by the examining pediatrician) (20), functional abnormalities (1) and findings in newborn screening (1). **CONCLUSIONS:** Investigators should establish, in advance, the exclusion criteria to be used in programs, such as malformation surveillance programs or pregnancy registries, whose findings are based on a review of the routine examinations in medical records. It is essential that the same criteria be used in evaluating the drug-exposed and the unexposed comparison group. *Birth Defects Research (Part A) 91:807–812, 2011.* © 2011 Wiley-Liss, Inc.

Key words: exclusion criteria; malformations; teratogens

INTRODUCTION

The rate of occurrence of malformations in newborn infants is the most common outcome tabulated in evaluating the fetal effects of any potential teratogenic exposure during pregnancy. The methodologies used to identify malformations can be as divergent as a separate study examination in which specific features are sought and specific measurements are made (Méhes et al., 1973; Leppig et al., 1987; Mills et al., 1988) or a review of the more varied findings recorded by the examining private pediatricians in the medical record of the exposed infants (Needleman et al., 1984; Holmes et al., 2008).

When establishing the frequency of malformations in newborn infants, criteria must be established in advance regarding the physical features that are a significant structural abnormality (i.e., a major malformation). If the evaluation is for the presence of a group of major malformations and minor anomalies, such as the nose hypoplasia and anteverted nostrils in phenytoin- or phenobarbital-exposed infants (Holmes et al., 2001), the special examination or record review can record the presence of those potential outcomes, not just major malformations. In the case of pregnancy registries that focus on the identification of only major malformations in a review of the medical records of infants exposed during pregnancy

Table 1
Malformations Including Those that were Due to
Gene Mutations and Chromosome Abnormalities

1. Included (n = 19)	a) heart defects (9)
	- hypoplastic left heart syndrome (2)
	- transposition of great arteries (3)
	- ventricular septal defect (2), membranous type and conoventricular type
	- double outlet right ventricle (1)
	- tricuspid atresia (1)
	b) cleft palate (2)
	c) congenital diaphragmatic hernia (1)
	d) epispadias (1)
	e) microtia (1)
	f) renal agenesis, bilateral (1) (elective termination)
	g) sacrococcygeal teratoma (1) (elective termination)
	h) veno-venous malformation of liver (1)
	i) multiple congenital anomalies of unknown etiology (2)
2. Excluded (n = 10)	a) genetic disorders (4)
	i) congenital adrenal hyperplasia
	ii) glutaric aciduria type II in association with polycystic kidney disease
	iii) polydactyly, postaxial, type B in infant born to Nigerian parents
	(iv) skeletal dysplasia[a] (elective termination)
	b) chromosome abnormalities (6)
	i) trisomies 21 (4)
	ii) trisomy 13 (2)

The numbers in parentheses indicate the number of affected infants.

[a]The skeletal dysplasia was spondyloepiphyseal dysplasia congenita, which was associated with a mutation in the COL2A1 gene.

(Holmes et al., 2008), the study personnel must have a set of exclusion criteria to evaluate the many different physical features that the examining pediatrician might record in the examination findings. To be as informative and unbiased as possible, the pregnancy registry should include an internal comparison group (i.e., controls) whose examination findings will be evaluated in the same fashion as those of the exposed infants.

To quantify this inclusion and exclusion process, the physical findings recorded in the medical record by the examining pediatricians in a consecutive series of 1000 births and elective terminations for anomalies have been reviewed to document the types of physical features recorded in routine examinations. Criteria have been developed for the features that are to be considered a malformation and those that should be excluded.

MATERIALS AND METHODS

This project was performed within the context of the Active Malformations Surveillance Program, which was established at the Boston Lying-In Hospital on February 16, 1972, and has been performed since then, except for a hiatus from February 15, 1975 until December 31, 1978, because of a lack of office space (Nelson and Holmes, 1989; Peller et al., 2006). The surveillance program moved to the new Brigham and Women's Hospital in 1981, which was formed when the Boston Lying-In Hospital merged with three other hospitals. This survey has been conducted 6 days a week and on holidays by research assistants who read the findings recorded by the examining physician in the medical record of each liveborn and stillborn infant. Malformations identified by prenatal studies and autopsies of pregnancies terminated electively have also been reviewed and tabulated. In this analysis, a *malformation* was defined as a structural abnormality with surgical, medical, or cosmetic importance.

The senior research assistant (M-N.W.) identified each infant born at this hospital for a consecutive sample of 1000 liveborn and stillborn infants and elective terminations for anomalies between January 1, 2008, and February 18, 2008. During that study period, 30 to 40 pediatricians could have been examining one or more infants each day. The features recorded in the medical records of liveborn infants were those identified between birth and discharge, but not later than 5 days of age. Birth to 5 days of age had been established as the time window for ascertainment in the first 3 years of this surveillance program (1972 to 1975), when routine discharge after a vaginal delivery was the fifth postpartum day. In recent years, most healthy infants have been discharged on the first or second postpartum days. The findings in infants born prematurely, who were hospitalized for several days or weeks, were restricted to findings recorded in the first 5 days of life. Stillborn infants and pregnancies terminated because of anomalies detected in prenatal testing are included. The presence of malformations was established by postmortem examinations.

The presence of an associated chromosome abnormality was determined from a review of the reports from chromosome analysis. The presence of a specific genetic diagnosis was established from a review of the reports of the pediatricians and consultations by geneticists, endocrinologists, surgeons, and other specialists. The results of mutation analyses and other diagnostic tests were used to confirm some diagnoses whenever available.

The specific types of physical features to be excluded were established in advance. This exclusion was based on our previous experience in this project with identifying the presence of minor anomalies and normal variations (Holmes et al., 1987; Leppig et al., 1987), birth marks (Alper and Holmes, 1983), and genetic abnormalities (Nelson and Holmes, 1989; Rasmussen et al., 1996; Holmes et al., 1997; Lin et al., 1998) in systematic study examinations.

RESULTS

The presence of a physical finding to be either included as a malformation or excluded was recorded in the initial pediatrician's examination of 240 (24%) of the 1000 infants whose medical records were reviewed; 29 (2.9%) of the 1000 infants had a malformation. These 28 malformations included four that were attributed to genetic disorders and six that were associated with chromosome abnormalities that excluded as not known to be caused by exposures to teratogens (Table 1). In addition, eight other types

Table 2
Frequency of Physical Features Recorded in Medical Records of 1000 Consecutive Liveborn and Stillborn Infants
and Elective Terminations for Fetal Anomalies

Physical features	No. per 1000 (%)	Published prevalence rates	References	Examples
Include:				
Malformations (Listed in Table 1)	18 (1.8)	2.2% at birth to 5 days of age	Nelson and Holmes, 1989	Transposition of great arteries, cleft palate, microtia
		2.0% at birth	Van Regermorter et al, 1984	
Exclude:				
1. Genetic disorders (listed in Table 1)	4 (0.4)	0.07%	Nelson and Holmes, 1989	Skeletal dysplasia, polydactyly, postaxial, type B
2. Chromosome abnormalities (listed in Table 1)	6 (0.6)	0.02%	Nelson and Holmes, 1989	Trisomies 21, 18, and 13
3. Minor anomalies	65 (6.5)	40%, 16%	Leppig et al, 1987; Méhes et al, 1973	Syndactyly of toes 2–3, transverse palmar crease
Example: sacral dimple	28 (2.8)	0.09% to 1.2%	Leppig et al, 1987; Méhes et al, 1973; Marden et al, 1964	
4. Birth marks	110 (11)	8%, all types	Alper et al, 1983	Hemangiomas, nevocellular nevi
Example: Mongolian spot	70 (7)	4.8% white, 88.7% African American	Alper et al, 1983	
5. Positional deformities	6 (0.6)	9.9%	Van Allen et al, 1994; Graham, 2007	Torticollis, hip dislocation in infant in breech position
6. Prematurity-related	5 (0.5)	24% of infants with birth weight < 1500 gm	Herrman et al, 2009	Patent ductus arteriosus in infant less than 36 weeks gestational age
7. Physiologic findings	4 (0.4)	Not established	Rojuin et al, 1995	Muscular ventricular septal defect
8. Ultrasound-only findings	20 (2)	Not established	Kitchens and Hernden, 2009	Hydronephrosis, absence of one kidney
9. Functional abnormalities	1 (0.1)	0.3%	White, 2004	Failed hearing test
10. Findings in newborn screening	1 (0.1)	Not established	Levy and Albers, 2000	Infant has elevated level of phenylalanine, a sign of phenylketonuria
Total	240 (24)			

of physical findings were excluded as not being a malformation: (1) minor anomalies and normal variations; (2) birth marks; (3) positional deformities; (4) prematurity-related features; (5) physiologic findings; (6) abnormalities detected only by prenatal ultrasound and not by the examining pediatrician at the time of the infant's birth ("ultrasound only"); (7) functional abnormalities, such as a failed hearing test; and (8) findings in newborn screening (Table 2).

The definitions of and rationale for these exclusions were established as follows.

Genetic Disorders

Four of the 1000 infants surveyed had malformations that are features of genetic disorders (Table 1). These malformations were attributed to mutations with either autosomal dominant, autosomal recessive, or X-linked patterns of inheritance, as described in Online Mendelian Inheritance in Man (Boyadjiev and Jabs, 2000). An estimate of the frequency of these disorders was established among 69,277 liveborn and stillborn infants and elective terminations for anomalies identified in the second trimester of pregnancy during 1972 to 1974 and 1979 to 1985 (Nelson and Holmes, 1989) in the Active Malformations Surveillance Program at Brigham and Women's

Hospital in Boston. Forty-eight of 69,277 infants (0.069%) had malformations attributed to single mutant genes.

Chromosome Abnormalities

Six infants had a chromosome abnormality, each of which was a trisomy. These abnormalities were identified in routine chromosome analysis with Giemsa staining. Trisomies, as well as deletions and unbalanced translocations, would be identified by these routine studies. In the survey of 69,277 consecutive infants born at this hospital (Nelson and Holmes, 1989), 157 malformed infants (0.2%) had a chromosome abnormality. This rate is lower than the overall rate of all chromosome abnormalities in newborn infants, such as 0.8% in the survey of 34,910 newborn infants (Nielsen and Wohlert, 1991). This lower prevalence rate reflects the fact that common sex chromosome abnormalities, such as 47,XXY and 47,XXX, often do not have associated physical abnormalities. Human teratogens have not been shown to cause trisomies.

Minor Anomalies

Minor anomalies are structural findings that do not have surgical, medical, or cosmetic importance. In the pioneering study by Marden et al. (1964), the frequency of minor anomalies was set as 4% or less, whereas the

term *normal variation* was used for minor physical features more common than 4%. Systematic study examinations of newborn infants, using this definition and following a study examination protocol, identified minor anomalies in 16.3% of 4589 infants in Györ, Hungary (Méhes et al., 1973) and in 39.9% of 4305 infants in Boston, Massachusetts (Leppig et al., 1987). The study examination in Boston looked for a longer list of minor anomalies.

Minor anomalies and normal variations recorded by some, but not all, examining pediatricians were excluded because there was no systematic or consistent search for the presence of these findings. Previous studies have shown that the reproducibility of finding minor anomalies by two examiners of the same infant have been poor. For example, two examiners of the same 444 infants born at this hospital, using the same definitions and an examination protocol, often did not record the same findings. They had poor agreement for 75% of the features evaluated, good agreement for 19.8%, and excellent agreement for only 5.2% of the features (Holmes et al., 1987).

Birth Marks

Birth marks were defined as a visible change in the skin, which includes a wide variety of entities: hemangiomas, nevocellular nevi, café au lait spots, depigmented nevi, and mongolian spots (Alper and Holmes, 1983). The birth mark recorded most frequently was the mongolian spot in 7% of the infants examined (Table 2).

The term *mongolian spot* is archaic and inaccurate but well established. It is a brown-black to blue-black patch with indistinct margins that is present most often on the sacrum and the buttocks. The size varies from a few centimeters to more than 10 cm. The mongolian spot has no medical significance. The prevalence rate varies dramatically among newborn infants with different racial backgrounds: 89% in African American infants and 5% in white infants (Alper and Holmes, 1983).

In general, birth marks have not been shown to be an effect of human teratogens. One exception was the increased frequency of infantile hemangiomas in infants exposed to the prenatal diagnosis procedure chorionic villus sampling (CVS) compared with infants exposed to amniocentesis (Kaplan et al., 1990).

Positional Deformities

Positional deformities are not associated with structural abnormalities; rather, they are normally formed physical features that have been distorted by exogenous forces, such as hip dislocation caused by the growth of an infant in a breech presentation within the mother's pelvis or an abnormal skull shape caused by pressure on the skull of fetuses crowded together in multiple gestations (Van Allen et al., 1994; Graham, 2007). In a systematic examination of infants of diabetic mothers and unexposed controls, mild positional deformities or deformations were common (9.9%) in both groups (Van Allen et al., 1994).

Prematurity-Related Physical Features

Prematurity-related physical features are findings that are more common in infants less than 36 weeks' gestational age, such as the patent ductus arteriosus and undescended testes. For example, 95 of 390 infants (24%) who weighed less than 1500 gm on admission to a newborn intensive care unit had a patent ductus arteriosus (Herrman et al., 2009).

Physiologic Findings

Physiologic findings are features that are part of the spectrum of normal. One example is the small muscular ventricular septal defect (VSD), which is very common and usually closes spontaneously within the first year of life. For example, echocardiograms of 1053 consecutive newborn infants in Israel showed that 56 (5.3%) had muscular VSDs (Rojuin et al., 1995). Only 10% of the affected infants had a heart murmur; 88.9% of the muscular VSDs had closed spontaneously by 10 months of age. Although we excluded almost all muscular VSDs, one large enough to produce congestive heart failure in a newborn infant would be considered a malformation, and not a physiologic benign physical feature.

Hydronephrosis, Absence of One Kidney, Megaureter, and Duplicated Ureter

Hydronephrosis, absence of one kidney, megaureter, and duplicated ureter are structural abnormalities of the urinary tract that which are often detected prenatally by ultrasound screening (Kitchens and Hernden, 2009). Although this screening is common, it is not performed systematically in 100% of pregnancies with the same equipment being used at the same period of gestation by sonologists with a similar, high level of experience. In addition, the detection rate is much less when the woman being screened is obese, which is a common confounder in prenatal screening. Therefore, we excluded genitourinary anomalies that were detected only by prenatal ultrasound examination and not by the examining pediatrician.

There are situations in which the examining physician could detect a genitourinary anomaly in a newborn infant. For example, the physician could see wrinkled skin on the abdomen as a feature of prune belly syndrome, which is attributed to urethral obstruction and enlargement of the bladder that prevents normal development of the abdominal muscles (Greskovich and Nyberg, 1988). Another example is when a horseshoe kidney or the absence of one kidney is identified with deep abdominal palpation by the physician examiner (Museles et al., 1971). If these genitourinary anomalies, including hydronephrosis, are not detected prenatally by ultrasound screening or the examining pediatrician at the infant's birth, they may be identified when the infant is older by imaging studies performed because of the occurrence of urinary tract infections.

Functional Abnormalities

Functional abnormalities, such as a failed test of hearing, were not considered a malformation. Newborn screening for hearing loss has been shown to identify a significant deficit in 0.3% of newborn infants (White, 2004), most of whom have no structural ear malformations. However, if the infant with a hearing loss had a malformed external ear, that deformity would be included as a malformation.

Findings in Newborn Screening

Findings in newborn screening (Levy and Albers, 2000), such as phenylketonuria, cystic fibrosis, or an abnormal hemoglobin, were not considered to be malformations.

DISCUSSION

This analysis of the physical findings recorded in the medical records of 1000 consecutive newborn infants showed that notable physical features, including malformations, birth marks and minor anomalies, were common and occurred in 24% of the infants. This high frequency emphasizes the importance of establishing a systematic method for deciding which features to include as malformations and which ones to exclude. Because the more minor features such as minor anomalies, birth marks, and prematurity-related findings were approximately 10-fold more common than malformations, it is particularly important to define and identify each component of this larger group.

The suggested list of exclusion illustrates the arbitrariness of what constitutes a malformation. The arbitrariness is balanced by using the same criteria in evaluating the findings in both the exposed infants and the unexposed comparison (i.e., control) infants. The clinician making the decisions to include or exclude should be unaware of the exposure status of each infant. The arbitrary decisions, of course, affect the baseline prevalence rate. Consider, for example, the effects of the arbitrary decision to exclude urinary tract anomalies, such as hydronephrosis, detected only by prenatal ultrasound screening and not by the examining pediatrician. Using the exclusion criteria proposed in this study, 1.8% of the 1000 infants surveyed had a malformation that could be caused by an exposure to a teratogenic drug. If the 20 infants with prenatally detected ''ultrasound only'' abnormalities, such as hydronephrosis (Table 2), were included as malformations, then the total baseline prevalence rate of malformations would be doubled, specifically 3.8% and not 1.8%. The effects of the inclusion and exclusion processes underscore the importance of including an unexposed comparison group in every study of potential teratogens. Of note, a review of the medical records of 12 infants considered by prenatal ultrasound examination to have hydronephrosis in subsequent follow-up evaluations in the first year of life showed that 58% did not have a significant urinary tract abnormality.

One objective of this study was to provide the definitions needed for identifying major malformations and for distinguishing them from the more common physical features that are not major structural abnormalities. The findings in an examination of an exposed or unexposed control infant at birth is common outcome used in pregnancy registries, but it has limitations. The apparently normal infant at birth could develop, when a few months older, a heart murmur that reflects a significant heart defect not identified previously. Alternatively, when older the normal newborn could develop a urinary tract infection in the evaluation of which imaging studies would identify the presence of a major malformation of the urinary tract. Another example is the infant with three or more minor anomalies who has an increased risk for having associated major malformations (Méhes et al., 1973; Leppig et al., 1987). This infant with several minor anomalies, when older, could be found to have a specific dysmorphic syndrome or an associated chromosome deletion or duplication, which was not recognized at birth. These subsequent diagnoses would be identified if the surveillance of the exposed and unexposed comparison group (controls) was extended to an older age group. However, follow-up surveillance is not a realistic option for most pregnancy registries.

The findings recorded in routine medical examinations of newborns have been used to assess the teratogenicity of exposures as diverse as the potential fetal effects of lead (Needleman et al., 1984) and the anticonvulsant drug lamotrigine (Holmes et al., 2008). Needleman et al. (1984) tabulated findings from the physicians' examinations in the medical records of newborn infants in 5183 consecutive deliveries. They recorded the presence of major and minor anomalies, hydrocele, and undescended testicles. They found a significant relationship between the levels of lead in blood samples from the umbilical cords of these infants and the rate of occurrence of ''minor congenital anomalies.'' Because these examinations were not standardized, the frequency with which a specific minor feature, such as hemangiomas and skin tags, would vary with the style of the examining pediatrician. As a result, there would be underreporting of common findings. For example, the frequency of skin tags and all types of hemangiomas in the special study examinations at the same hospital (Leppig et al., 1987; Alper and Holmes, 1983) were 2.08% and 70.46%, whereas the frequencies in the lead-exposed infants (Needleman et al., 1984) evaluated by the findings recorded in nonstandardized examinations were 1.2% and 1.4%, respectively. This significant underreporting of common findings illustrates the limitations of using nonstandardized examination findings in the assessment of teratogen-exposed infants. In contrast, the likelihood of identifying the presence of major malformations in both systematic study examinations and routine pediatrician examinations is much higher.

Regarding the possible teratogenesis of lamotrigine, the medical records of infants exposed in the first 14 weeks of gestation, whose mothers had enrolled in the North American AED (antiepileptic drug) Pregnancy Registry, were reviewed to identify malformations (Holmes et al., 2008). The minor anomalies and birth marks were excluded, using the exclusion criteria outlined in this analysis. Focusing only the occurrence of major malformations, a significantly increased frequency of isolated cleft palate was noted.

Two other factors to consider in using the findings in routine newborn examinations in evaluating potential teratogenic exposures are the potential for observer bias and the time window for identifying physical features.

The term *observer bias* means that the observer has a focus on specific physical findings that are more likely to be seen. For example, a study of infants exposed during pregnancy to anticonvulsant drugs showed that the examiners were more likely to see the expected facial features of nose hypoplasia and anteverted nostrils that had been identified in systematic study examinations done before these distinctive facial features had been recognized (Harvey et al., 2003). Another example identified in this study of infants born in 2008 was the fact that the pediatricians performing routine examinations appeared to have a specific concern to identify the presence of a sacral dimple. (A sacral dimple is a dimple with a visible base, not a sinus tract, in the midline over the sacrum and

between the buttocks.) Twenty-eight infants (2.8%) were considered to have a sacral dimple. Many infants with this finding had ultrasound examinations of the lumbar spine to look for the presence of an abnormality of the spinal cord. Although the pediatricians at this hospital seemed to consider the sacral dimple a marker for an underlying abnormality of the spinal cord, systematic studies (Abu Sneineh et al., 2002) have shown no evidence of a significant association between the presence of a sacral dimple and abnormalities of the adjacent spinal cord.

The term *time window* refers to the age of the infant when a physical feature was detected. The time window can range from the infant's day of birth, the day of birth through five days of age (Nelson and Holmes, 1989), day of birth to 12 weeks of age (Holmes et al., 2008), and day of birth to one year of age (Correa-Vissasenor et al., 2003). In general, the prevalence rates of malformations have been approximately 2% at birth (Nelson and Holmes, 1989; Van Regemorter et al., 1984), 3% at 1 year of age (Correa-Vissasenor et al., 2003), and higher at an older age (Say et al., 1973). An illustration of the effect of the time window is the failure to identify initially significant physical features in infants at birth. For example, very premature infants are often covered extensively at birth to maintain their body temperature. These coverings are removed when the infants are older and can reveal significant abnormalities, such as absence of the distal portion of the fifth finger (McGuirk et al., 2001) or virilization of a female infant (Travitz et al., 2005).

The prevalence of malformations in newborn infants surveyed at this hospital previously was 2.24% (Nelson and Holmes, 1989). After subtracting the frequency of chromosome abnormalities and genetic disorders, the prevalence rate was 1.62% among infants born to mothers who had planned to deliver at this hospital. The prevalence rate identified in this survey was higher (2.8%), because the sample included infants whose mothers transferred their care during pregnancy after the prenatal detection of an abnormality in the fetus at another health care facility.

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