Limb Deficiencies in Newborn Infants

Caroline K. McGuirk, MPH*; Marie-Noel Westgate, MEd‡; and Lewis B. Holmes, MD*‡§

ABSTRACT. *Objective.* **The prevalence rate of all types of limb reduction defects in general and those that potentially are caused by vascular disruption in particular is needed to provide a baseline for the evaluation of infants who are exposed in utero to teratogens that cause vascular disruption. The objective of this study was to determine this prevalence rate.**

Methods. **All infants with any limb deficiency among 161 252 liveborn and stillborn infants and elective terminations were identified in a hospital-based Active Malformations Surveillance Program in Boston in the years 1972 to 1974 and 1979 to 1994. An extensive search was made to identify infants who were missed by the Surveillance Program; an additional 8 infants (7.3% of total) were identified. The limb reduction defects were classified in 3 ways: 1) by the anatomic location of the defect, that is longitudinal, terminal, intercalary, etc; 2) for infants with absence/hypoplasia of fingers or toes, a tabulation of which digit or digits were affected; and 3) by apparent cause.**

Results. **The prevalence rate for all types of limb deficiency was 0.69/1000. The apparent causes included single mutant genes, familial occurrence, and known syndromes (24%); chromosome abnormalities (6%); teratogens (4%); vascular disruption (35%); and unknown cause (32%).**

Conclusions. **A hospital-based surveillance program can be used to establish the prevalence of limb reduction defects, if ascertainment is extended to include elective terminations for fetal abnormalities. An apparent cause can be established for most limb defects when the clinical findings are used rather than reliance only on the *International Classification of Diseases, Ninth Revision,* codes of the discharge diagnoses. The prevalence rate of limb reduction defects as a result of presumed vascular disruption was 0.22/1000. *Pediatrics* 2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e64; *limb deficiency, vascular disruption.***

ABBREVIATIONS. CVS, chorionic villus sampling; BWH, Brigham and Women's Hospital; *ICD-9, International Classification of Diseases, Ninth Revision.*

From the *Genetics and Teratology Unit, Pediatric Service, Massachusetts General Hospital, Boston, Massachusetts; the ‡Department of Newborn Medicine, Brigham and Women's Hospital, Boston, Massachusetts; and the §Department of Pediatrics, Harvard Medical School, Boston, Massachusetts.
Received for publication Nov 20, 2000; accepted May 29, 2001.
Reprint requests to (C.K.M.) Genetics and Teratology Unit, Warren 801, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114-2696. E-mail address: cmcguirk@partners.org

Limb deficiencies are a widely known outcome associated with teratogenic exposures during pregnancy, such as thalidomide,[1] misoprostol (prostaglandin E_1 analog),[2] and the prenatal diagnosis procedure chorionic villus sampling (CVS).[3–5] Each of these teratogens produces a distinctive pattern of limb defects. Specifically, infants who are damaged in utero by thalidomide have a symmetrical pattern of deficiency (or polydactyly) on the preaxial side of both arms and legs.[1] By contrast, infants who are exposed early in pregnancy to misoprostol and CVS have asymmetrical digit loss, constriction rings, and syndactyly. These abnormalities are attributed to the process of vascular disruption in limb structures that had formed normally and include defects referred to as the amniotic band syndrome.

The recognized causes of vascular disruption in the fetus, in addition to the prostaglandin misoprostol administered in the second month of pregnancy[2] and CVS, especially before 10 weeks' gestation,[3–5] include exposure to ergotamine,[6] dilation and curettage,[7] and trauma to the abdomen (and placenta).[8] This means that limb reduction defects that are labeled as amniotic band syndrome can have 1 of several different underlying causes. Experimental studies[9] suggest that the sequence of events that leads to these similar deformities is hypoxia, followed by endothelial cell damage, hemorrhage, tissue loss, and reperfusion. In addition to digit defects, the phenotypic effects of these exposures may include arthrogryposis[10] and bowel atresia.[11,12]

Previous studies of the frequency of limb reduction defects were based on large populations, such as an entire country (eg, Sweden),[13] or a large region, (eg, eastern France)[14] or a province (eg, British Columbia).[15] Unfortunately, the details on the specific deficiencies in each affected infant are not always available in a large population survey. Another problem is the lack of a consensus as to the best way to classify limb reduction defects.[16] In particular, should there be a category for limb deficiencies attributed to amniotic bands? In studies of the limb reduction defects associated with CVS, some authors excluded this group[17] and others included it.[18] However, several reported CVS-exposed infants with limb reduction defects have had absence of the distal portion of the third finger[19] (J. Zachary, personal communication, January 3, 2000; D. Wilson, personal communication, September 22, 1999), fingers 2 and 3,[5,20] and fingers 3 and 4[20] with or without tapering and stiffness, which could be considered consistent with the diagnosis of the amniotic band syndrome. Therefore, if a deficiency of 1 or 2 digits can be

caused by exposure to a teratogen, then these specific outcomes must be included in the assessment of the fetal risks from these exposures.

We used an active hospital-based malformations surveillance program of newborn infants to establish the frequency of all types of limb deficiency, including those caused by vascular disruption. We also included a tabulation of absence/hypoplasia of any single digit or any combination of digits in the hands and feet (Fig 1).

METHODS

This study used the data that had been obtained by the Active Malformations Surveillance Program at Brigham and Women's Hospital (BWH), the methodology of which has been described previously.[21] The study period was 1972 to 1974 and 1979 to 1994, during which time all infants with major malformations were identified among liveborn and stillborn infants and all elective terminations performed in the second trimester because of suspected fetal abnormalities. The initial study period was February 16, 1972, to February 15, 1975, but is referred to as 1972 to 1974; the surveillance program was not conducted from February 16, 1975, to December 31, 1978, because of a lack of space and funds.

A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance. A limb deficiency was defined as the absence or hypoplasia of a phalanx, metacarpal or metatarsal bone, or portion of any long bone large enough to produce a significant deformity that could be detected at birth by the examining physician. Excluded from this tabulation was mild shortening of digits as a result of brachydactyly as an isolated finding or as part of a skeletal dysplasia, curvature (eg, clinodactyly of the fifth finger or bowing of the tibia due to fetal positioning), and digits considered "hypoplastic" in appearance but not shortened. A product of conception delivered by a destructive procedure to terminate the pregnancy was excluded when the presence of the deficiency diagnosed in prenatal sonography was not confirmed in the postmortem examination. The term "isolated limb reduction defect" was used to refer to the infant who had no major malformations involving nonlimb structures; the infant with an isolated limb reduction defect could have abnormalities in 1 or more limbs, including arms and legs. The infant with multiple malformations had major malformations of both limb(s) and nonlimb structures.

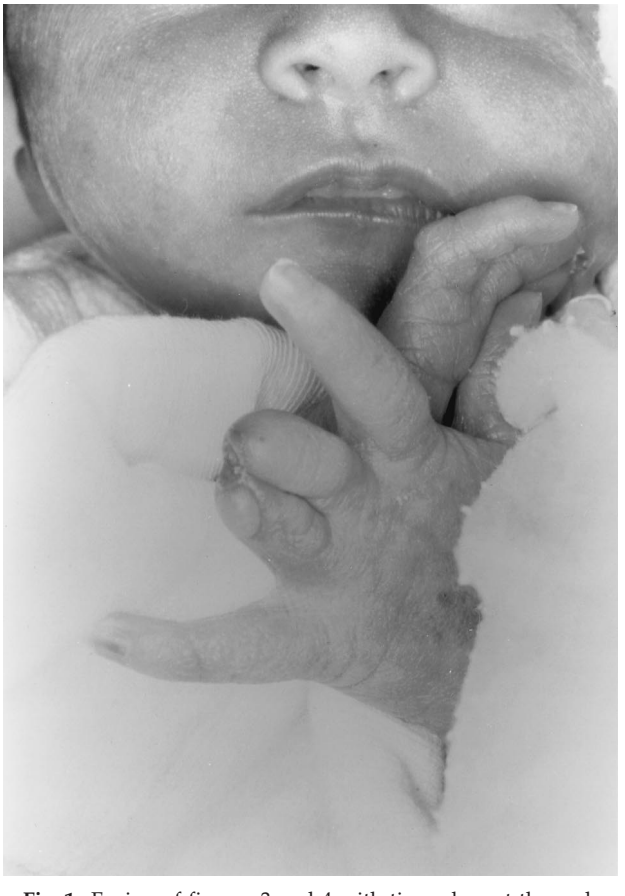

Fig 1. Fusion of fingers 3 and 4 with tissue loss at the end.

In the Active Malformations Surveillance Program, the index cases were identified from the review of the findings either in the initial examinations by the pediatricians of each liveborn infant or by the pathologist at autopsy or the surgeon in an operation. In addition, a questionnaire was administered by a research assistant to the mother postpartum to review the pregnancy, medical, and family histories. Other sources of information were chromosome analyses; diagnostic studies, such as ultrasound, magnetic resonance imaging, and computed tomographic scans; and the report of all consultants who had evaluated each affected infant. Clinical diagnoses were established from a review of the clinical and laboratory findings, rather than by reliance on the diagnosis coded on discharge or on birth certificates.

To be an index case in this study, the infant with the limb reduction defect had to have been identified by surveillance personnel within the first 5 days of life, even if the diagnosis was not clarified. The period of 5 days was established in the first study period, 1972 to 1974, when the infants who were born after a vaginal delivery were discharged from the hospital routinely on the fifth day postpartum.

All infants in the computerized database with diagnoses of *International Classification of Diseases, Ninth Revision (ICD-9)* codes 755.2 to 755.4 were identified; these codes designate reduction defects of the upper limbs, lower limbs, and unspecified locations. The surveillance program questionnaire was used as the primary source of information as to the sex, gestational age, race, possible multiple gestations, exposure to a known teratogen, and family history. When this information had not been recorded at the time of the initial enrollment, it was obtained from the infant's and the mother's medical records and the surgeon's records. Photographs and radiographs taken of any of these infants at birth were reviewed to confirm the anatomic findings. When a relative was reported to have a limb reduction defect of any type, the family was contacted and asked to provide more details. The findings in relatives were evaluated to identify any hereditary disorder.

In an effort to find infants who were born at BWH and who had been missed by the surveillance program, 8 local hand surgeons and plastic surgeons were asked to provide a list of their patients who had been born in the study years 1972 to 1974 and 1979 to 1994 and had diagnoses in *ICD-9* codes 755.2 to 755.4. The medical record department at the adjacent Boston Children's Hospital also was asked to provide a list of patients who were seen there and who had any of the diagnoses of interest. The BWH medical records were reviewed to determine whether the infants with that last name and identified elsewhere had been born at BWH on that date of birth. When the infants were found to have been born at BWH, the medical records of the surgeon's office, Boston Children's Hospital, and BWH were reviewed to establish the phenotype, the apparent cause, and family history. In addition, letters were sent to all families of affected infants who had unknown causes or who were missed on surveillance to invite them to come to the hospital for a study-related examination at no charge.

After all index cases had been identified, they were subdivided into those whose mothers had always planned to deliver at BWH (called nontransfers) and those who had transferred to BWH for care after the prenatal detection elsewhere of a fetal abnormality (called transfers). Information about exposure to any prenatal testing was obtained from the interview of the mother by the surveillance study personnel and the mother's medical record. In addition, the list of all women who had had CVS in the study years through the BWH prenatal diagnosis program was reviewed for the names of women whose children had been identified as having a limb reduction defect.

For the anatomic classification, a nosology that combined the systems of Kallen,[13] Stoll et al,[14] and Froster and Baird[15] was used. The definition used for a longitudinal defect was either absence or hypoplasia of the first (and second) digit or absence or hypoplasia of the fifth (and fourth) digit. A longitudinal central deficiency was absence or hypoplasia of digit 3 alone, 2 and 3, or 3 and 4. The

term "terminal transverse" was used for absence or hypoplasia of digits 1 to 5, 2 to 5, or 1 to 4. (Table 1)

To record separately absence or hypoplasia of 1, 2, 3, 4, and 5 digits in the hands or feet and possible combinations, we used a separate classification for isolated limb reduction defects involving the hands only (Table 2) and the feet only (Table 3). In these tabulations, an infant with similar deficiencies in both hands but with different degrees of severity was classified as bilateral and by the pattern in the more severely affected hand. Infants with mixed defects, ie, different types of deficiencies, on each hand were classified by only 1 of these defects and are listed in the legends. Two infants had limb reduction defects involving the hands and feet; these are not included in either table.

The apparent cause assigned for each affected infant was based on the pregnancy history (for teratogenic exposures), family history, and a review of the infant's medical record that focused on the findings of the examining pediatricians, all consultants, and laboratory tests (Table 4). Those listed as being due to vascular disruption were limb reduction defects that either have been described in infants who have been exposed to a teratogen considered to have this effect, such as misoprostol and CVS, or have been produced in animal models of vascular disruption, such as clamping the uterine artery.[9] These phenotypes included terminal transverse limb defects with residual nubbins, Poland's anomaly, amniotic band syndrome, and Moebius syndrome, when limb reduction defects also were present.

RESULTS

Among the 161 252 liveborn and stillborn infants and elective terminations surveyed, 102 infants of nontransfers had diagnoses in *ICD-9* codes 755.2 to 755.4. None had been exposed to CVS; 1 had been exposed to misoprostol.[22] There were 82 exclusions: 2 infants with skeletal dysplasias, 4 with a type of brachydactyly, 71 maternal transfers, and 5 spontaneous abortions of <20 weeks' gestational age. Twenty percent of the index cases were from pregnancies that were terminated electively.

Affected Infants Not Identified by Surveillance

A total of 1167 children who were born in the study years and diagnosed as having a limb reduction defect (*ICD-9* codes 755.2–755.4) were identified in a review of medical records at 8 doctors' offices and in the medical records at the adjacent Boston Children's Hospital; 65 of those children had been born at BWH. Eight (7.3%) had a limb deficiency that had not been identified correctly by the Active Malformations Surveillance Program; 5 of these 8 infants were not identified by surveillance personnel, but their limb reduction defects had been noted by either the pediatrician or a consultant before the infant's discharge. Their limb defects were absence of fibula and toes 2 to 5, unilateral (1); hypoplasia of third metacarpal and phalanges of third finger, unilateral (1) (Fig 3); unilateral brachydactyly of fingers 2 to 5, as part of Poland anomaly (1); hypoplasia of toes 2 to 5, unilateral, as part of a multiple anomaly syndrome of unknown cause (1); and absence of fibula, unilateral, with normal toes (1). Three of these 8 infants were not identified because the findings of the limb deficiency either were not recorded at all or were not recorded until after 5 days of age: absence of distal phalanx of index finger (1) or fifth finger (1); absence of fifth finger (1). We reviewed the reasons that the infants were missed and took steps to try to prevent the same mistakes from happening again. For instance, the missed infant with the absent fibula and absent toes 2 to 5 had been born on a Friday afternoon and discharged on Monday morning between

TABLE 1. Anatomic Classification

	Prevalence (*n*/1000)	Arms (*n* = 77)	Legs (*n* = 20)	Arms and Legs (*n* = 13)
Amelia	0.006	0	1	0
Intercalary	0.06	5 (1*)	3 (1*)	2 (1†, 1*)
Meromelia				
Terminal transverse	0.19	24 (4*)	6 (1*)	0
Longitudinal				
Preaxial	0.14	21 (5†, 2*)	0	1 (1*)
Postaxial	0.08	8 (1*)	4	1
Pre and Post	0.05	7 (1†, 1*)	0	1
Central	0.06	3	4	2
Mixed	0.07	5	1	6 (2*)
Unspecified	0	0	0	0
Unclassifiable	0.03	4	1	0
Total	0.69			

Excludes all maternal transfers with fetal abnormalities, 5 spontaneous abortions of <20 weeks, all infants with skeletal dysplasia, and 4 infants with brachydactyly.
* Delivery by D and C.
† Delivery by infusion.

TABLE 2. Isolated Limb Reduction Defects in the Hands of 161 252 Infants Born at BWH During the Years 1972 to 1974 and 1979 to 1994

	Right	Left	Both
One finger			
No. 1	1 (1†)	2	1 (1†)
No. 2	1		
No. 3		1	1
No. 4			
No. 5	2	3	1§
Two fingers			
No. 1 and 2			
No. 2 and 3			1‖
No. 3 and 4			1*
No. 3 and 5			
No. 4 and 5	1		
No. 1 and 5			
No. 2 and 5			
Three fingers			
No. 1–3			
No. 2–4			
No. 3–5			
Four fingers			
No. 1–4		1 (1*)	
No. 2–5		3 (1*)	1¶
No. 1, 3–5		1	
Five fingers			
No. 1–5	3 (1‡)	5	1#

Infants were included in this table even when metacarpals were involved and when the only other malformation was syndactyly. Infants were included in this table when they had no other malformation beside the limb reduction defect that was limited to the hands.
* Presence of constriction bands.
† Presence of Fanconi's anemia.
‡ Presence of split hand.
§ Left hand, absent fifth finger; right hand, hypoplastic first finger.
‖ Left hand, brachydactyly of the third and fourth digits; right hand, brachydactyly of the second and third digits (Fig 2).
¶ Left hand, absence of the distal and middle phalanges of digits 2, 3, and 4 and hypoplasia of the distal and middle phalanges of the fifth digit and only approximately one half of the development of the proximal phalanges of all 4 digits; right hand, distal phalanges of the second and third digits are hypoplastic.
# Left hand, hypoplastic digits 1 to 5; right hand, hypoplastic digits 3 to 5.

TABLE 3. Isolated Limb Reduction Defects in the Feet of 161 252 Infants Born at BWH During the Years 1972 to 1974 and 1979 to 1994

	Right	Left	Both
One toe			
No. 1			
No. 2			
No. 3	2 (1* and 1†)		
No. 4			
No. 5			
Two toes			
No. 1 and 2			
No. 2 and 3			1 (1†)‡
No. 3 and 4			
No. 3 and 5			
No. 4 and 5			1§
No. 1 and 5			
No. 2 and 5			
Three toes			
No. 1–3			
No. 2–4			
No. 3–5			
No. 1, 2, 4	1		
Four toes			
No. 1–4			
No. 2–5	1		
No. 1, 3–5			
Five toes			
No. 1–5		2	

Infants were included in this table even when metatarsals were involved and when the only other malformation was syndactyly. Infants were included in this table when they had no other malformation beside the limb reduction defect that was limited to the feet.

* Presence of constriction bands.

† Presence of split foot.

‡ Right foot, absence of third digit; left foot, absence of digits 2 and 3.

§ Right foot, absence of digits 4 and 5; left foot, absence of fifth digit.

the reviews by surveillance personnel. At that time, surveillance was conducted only from Monday through Friday. Thereafter, it was conducted on Saturday as well. The addition of these 8 missed cases increased the number of infants of nontransferred mothers with some type of limb deficiency to 110, for a prevalence rate of 0.69/1000 (Table 1).

Anatomic Classification

Tabulation of anatomic classification (Table 1) showed that 1) limb reduction defects were much more common in the arms alone (77 [70%] of 110 deficiencies) than in the legs alone (18%) or both arms and legs (12%) and 2) in the arms, preaxial deficiencies, such as absent thumb, accounted for 27% of the deficiencies and terminal transverse limb reduction defects accounted for 31% of the deficiencies.

The separate tabulation of the absence or hypoplasia of 1 or more fingers and toes in infants with no other nonskeletal malformations showed that absence or hypoplasia of the fingers was much more common than absence or hypoplasia of the toes (Tables 2 and 3). In the hands, shortening or absence of all 5 fingers was the most common phenotype and was unilateral in 8 of the 9 affected infants (89%). Involvement of only the third finger alone or only fingers 2 and 3 occurred twice and once, respectively, in the 110 infants with limb deficiencies. No distribution of deficiencies of toes could be established because only 8 infants were affected. Only 1 infant had absence of the third toe with constriction bands as an isolated malformation.

Classification by Cause

Limb reduction defects that were associated with known hereditary disorders (15%), chromosome abnormalities (6%), specific malformation syndromes (5%), and unclassified but familial phenotypes (4%) accounted for 30% of the limb defects identified (Table 4). In addition, 3.9% of the infants had been exposed to recognized teratogens, either misoprostol[22] or maternal diabetes. Therefore, the balance (66%) had other causes, divided almost equally between vascular disruption (34%) and no recognized cause (32%), such as absent fibula.

There were difficulties with the etiologic classification because of associated characteristics. For example, 1 infant with a terminal transverse limb reduction defect that included residual nubbins had a similarly affected first cousin. Her deficiency could be classified by appearance as having been caused by the process of vascular disruption but also was listed (Table 4) as being familial. Another problem was the uncertainty as to whether the limb reduction defect in an infant of a diabetic mother was, in fact, attributable to the mother's diabetes, as there is no such established association.[23] The findings in this classification by cause confirm the significant degree of heterogeneity in the recognized causes of limb deficiencies.

CONCLUSION

This is the first report of the frequency of limb reduction defects attributable to the process of vascular disruption in a large population of newborn infants. The study benefited from the thorough evaluations of affected infants that made it possible to identify both the specific fingers or toes affected and the most likely underlying cause.

This study showed that a hospital-based malformations surveillance program can be used to determine the prevalence of all types of limb deficiency. However, to be complete, this type of program must include affected infants from elective terminations, as a significant number (20% in this study) of the affected fetuses identified were from pregnancies that had been terminated electively. It also must exclude infants who are born to women who had planned, before prenatal screening, to deliver at another hospital. If the maternal transfers had been included, then the prevalence rate would have been 1.1 per 1000 rather than 0.69/1000. There always is the chance that the surveillance program personnel will not identify an affected infant. However, this study showed that only 7.3% (8 of 110) of the affected infants were missed.

The prevalence rate determined (0.69/1000) is similar to the overall prevalence rates reported by Kallen[13] (0.68/1000), Stoll et al[14] (1.04/1000), and Froster and Baird[15] (0.6/1000). However, the period of time used for case ascertainment in each of these

TABLE 4. Limb Defects Classified According to Likely Pathogenesis

	Isolated (n = 58)	Multiple Anomalies (n = 52)	Total (n = 110)	Prevalence (n/1000)
Malformations				
Mendelian inheritance	10 (9%)	7 (6%)	17 (15%)	0.11
(eg, Fanconi anemia)	1†	1†, 1*, 1‡		
Familial occurrence	2 (2%)	2 (2%)	4 (4%)	0.02
(eg, uncle with split hand)		1*		
Chromosome abnormalities	0	7 (6%)	7 (6%)	0.04
(eg, tri 18, 4p-, 13q-)		1†, 2*, 1‡		
Known syndrome	0	6 (5%)	6 (5%)	0.04
(excludes amniotic bands; Moebius syndrome; Poland's anomaly; and terminal forearm, hand, and foot defects with nubbins)		1†, 1*		
Teratogens				
Infants of diabetic mothers (IDM)	1 (0.9%)	2 (2%)	3 (3%)	0.02
	1*			
Misoprostol-exposed (22)	0	1 (0.9%)	1 (0.9%)	0.006
		1*‡		
Presumed vascular disruption defects				
Amniotic band syndrome	7 (6%)	6 (5%)	13 (12%)	0.08
		2*		
Moebius syndrome	0	1 (0.9%)	1 (0.9%)	0.006
Poland's anomaly	0	3 (3%)	3 (3%)	0.02
Forearm defect with nubbins	4 (4%)	0	4 (4%)	0.02
	1*, 1‡			
Absent hand with nubbins	4 (4%)	0	4 (4%)	0.02
	1*, 1‡			
Foot defect with nubbins	1 (0.9%)	0	1 (0.9%)	0.006
Other similar phenotypes	9 (8%)	2 (2%)	11 (10%)	0.07
Unknown cause	20 (18%)	15 (14%)	35 (32%)	0.22
Total	1*	3†, 3*		0.69/1000

Excludes all maternal transfers with fetal abnormalities, 5 spontaneous abortions at <20 weeks, all infants with skeletal dysplasia, and 4 infants with brachydactyly.
* Delivery by D and C.
† Delivery by Infusion.
‡ Children whose malformations have more than 1 cause.

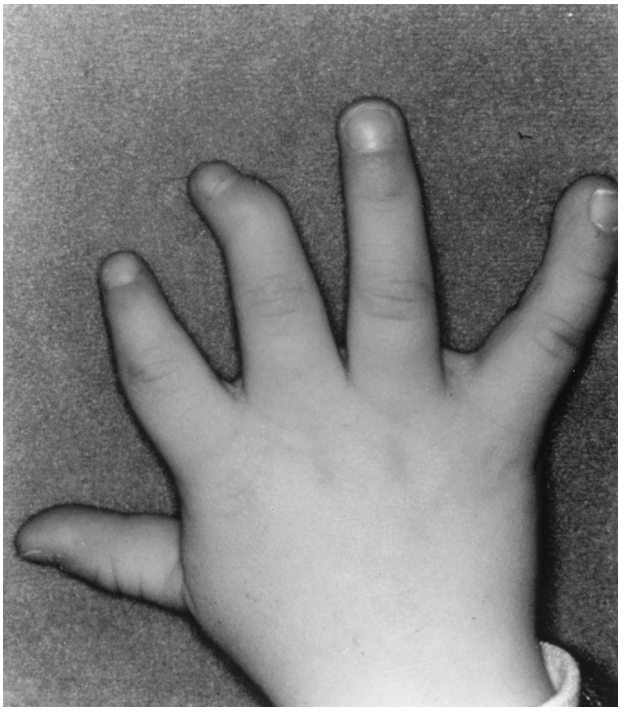

Fig 2. Shortening and tapering of the second and third finger in the right hand. There were similar changes in the third and fourth fingers of the left hand.

studies was greater than the first 5 days of life, the postnatal period of ascertainment used by our surveillance program.

A careful review of the clinical findings rather than reliance only on *ICD-9* codes was needed to delineate specific causes. For example, 22 infants had absence or hypoplasia of the thumb with or without hypoplasia of the radius; 14 of these infants had at least 1 other malformation in addition to the limb reduction defect. The causes of the limb reduction defects in the 22 infants established from the clinical review were as follows: 6 (27%) due to dominant or recessive genes, such as Holt-Oram syndrome (1), Fanconi's Anemia (3), split hand deformity (1), and thrombocytopenia-radial aplasia (1); 2 (9%) associated with maternal insulin-dependent diabetes; and 3 (14%) associated with chromosome abnormalities, eg, trisomy 18. No cause was determined for 11 (50%) of the infants with absence or hypoplasia of the thumb. The attribution of limb reduction defects to vascular disruption was based on the fact that similar phenotypes have been observed in infants who had had an exposure, such as CVS, misoprostol, and ergotamine, which are thought to produce limb deficiencies by the process of vascular disruption. In a specific infant without such an exposure, the clinician cannot prove that this process occurred, except indirectly when the fetal membranes show absence of the epithelium of the amnion, as occurs in the case of amnion rupture.[22] Even after the clinical review, no cause was apparent for 32% of these limb reduction defects. We realize that the cause of some limb reduction defects will never be identified. We also recognize that even

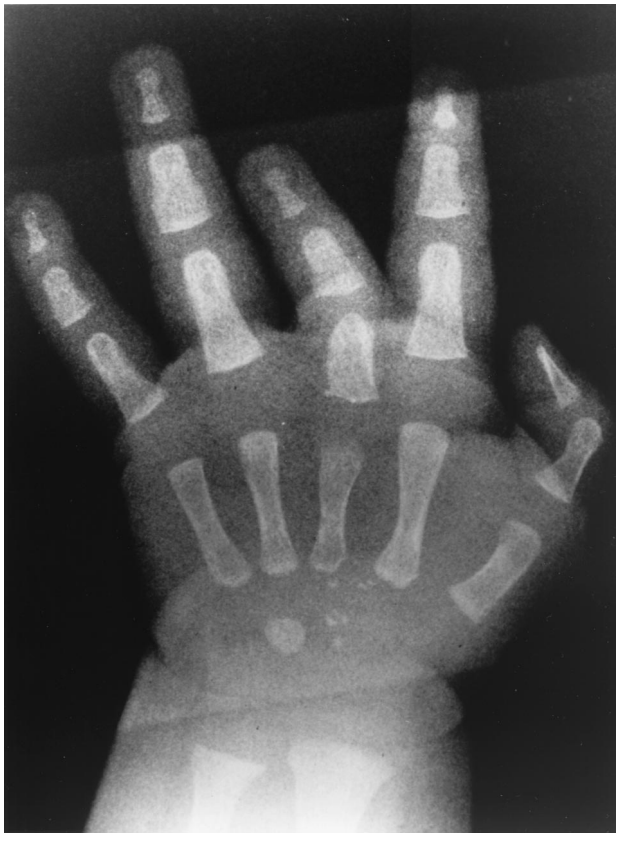

Fig 3. Radiograph of infant with hypoplasia of third finger, showing shortening of metacarpal and proximal phalanx. The initial description of this deformity was "a flexion deformity due to abnormal positioning." (This case was missed by the Surveillance review, as the more specific description by the consultant in plastic surgery was not noted.)

if a limb reduction defect is apparently caused by a vascular disruption, the factor that caused this disruption to occur often is not known.

This study showed that isolated limb reduction defects that involve 1, 2, or 3 digits can be identified by an active surveillance program and are common (16 of 110; 15% of all defects). Some of these infants had associated constriction rings and digit fusion, but most did not. Because both misoprostol-exposed[2,22] and CVS-exposed infants[5,19,20] (D. Wilson, personal communication, September 22, 1999, and J. Zachary, personal communication, January 3, 2000) have an increased frequency of limb reduction defects involving only 1 or 2 digits, including some with the appearance of the amniotic band type of defects, this baseline frequency could be particularly helpful to the study of infants who have had those exposures.

Both clinical[24,25] and experimental[9] studies of the amniotic band syndrome confirm the need for a classification of limb reduction defects that identifies the specific digits affected. Light and Ogden[24] and Czeizel et al,[25] in their respective reviews of 88 and 126 affected children, found that the hands were involved much more often than the feet and that the most frequently affected fingers were the third, fourth, and second, in that order. The animal model of fetal hypoxia, described by Webster et al,[9] showed that hypoplasia of digits 2 to 4 could be produced, including hypoplasia of only the distal portion of the middle finger, a finding observed among CVS-exposed infants with limb reduction defects[19] (J. Zachary, personal communication, January 3, 2000; D. Wilson, personal communication, September 22, 1999). This possible correlation of CVS exposure with a rare type of digit reduction defect underscores the importance of being able to identify this category in a study of the birth prevalence of limb reduction defects.

Additional progress will be made in the delineation of the causes of limb deficiencies when mutation analysis can be conducted routinely. For example, some of the infants whose only malformation is absence or hypoplasia of the thumb could have the Holt-Oram syndrome, as thumb deformities have been shown to be the only manifestation of some of the mutations in the TBX5 gene.[26]

ACKNOWLEDGMENTS

This study was supported by NIH Study #HD 33222 and the National Birth Defects Prevention Study, the National Center for Environmental Health, Centers for Disease Control and Prevention through a grant to the Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health and the Peabody Foundation, Boston.

We thank the many pediatricians, surgeons, pathologists, cytogeneticists, geneticists, and other consultants whose careful evaluations and diagnostic acumen contributed to the classification of the findings in the affected infants and fetuses. We also thank Drs Joseph Upton, Peter Waters, Barry Simmons, Richard Gelberman, Charles Hergrueter, Douglas Rothkopf, Richard Zienowicz, and Michael Goldberg for assistance in identifying infants who had limb defects and had been missed by the Active Malformations Surveillance Program at BWH.

REFERENCES

1. Kallen B, Rahmani TM-Z, Winberg J. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. *Teratology*. 1984;29:73–85
2. Gonzalez CH, Marques-Dias MJ, Kim CAE, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in the first trimester of pregnancy. *Lancet*. 1998;351:1624–1627
3. Firth HV, Boyd PA, Chamberlain P, MacKenzie IZ, Lindenbaum RH, Huson SM. Severe limb abnormalities after chorionic villus sampling at 56–66 days' gestation. *Lancet*. 1991;337:762–763
4. Firth HV. Chorion villus sampling and limb deficiency: cause or coincidence? *Prenat Diagn*. 1997;17:1313–1330
5. Burton BK, Schulz CJ, Burd LI. Spectrum of limb disruption defects associated with chorionic villus sampling. *Pediatrics*. 1993;91:989–993
6. Raymond GV. Teratogen update: ergot and ergotamine. *Teratology*. 1995;51:344–347
7. Holmes LB. Possible fetal effects of cervical dilation and uterine curettage during the first trimester of pregnancy. *J Pediatr*. 1995;126:131–134
8. Viljoen DL. Porencephaly and transverse limb defects following severe maternal trauma in early pregnancy. *Clin Dysmorphol*. 1995;4:75–78
9. Webster WS, Lipson AH, Brown-Woodman PDC. Uterine trauma and limb defects. *Teratology*. 1987;35:253–260
10. Hall JG. Arthrogryposis (AMC) associated with unsuccessful attempts at termination of pregnancy. *Am J Med Genet*. 1996;63:293–300
11. Van Allen MI. Structural anomalies resulting from vascular disruption. *Pediatr Clin North Am*. 1992;39:255–277
12. Bower C, Norwood F, Knowles S, Chambers H, Haan E, Chan A. Amniotic band syndrome: a population-based study in two Australian states. *Paediatr Perinat Epidemiol*. 1993;7:395–403
13. Kallen B. A prospective study of some aetiological factors in limb reduction defects in Sweden. *J Epidemiol Community Health*. 1989;43:86–91
14. Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in limb reduction defects. *Paediatr Perinat Epidemiol*. 1992;6:323–338
15. Froster UG, Baird PA. Limb reduction defects in over one million consecutive livebirths. *Teratology*. 1989;39:127–135
16. Froster UG. Academicians are more likely to share each other's tooth-

brush than each other's nomenclature [Cohen, 1982]. *Am J Med Genet*. 1996;66:471–474
17. Froster UG, Jackson L. Limb defects and chorionic villus sampling: results from an international registry, 1992–94. *Lancet*. 1996;347:489–494
18. Olney RS, Khoury MG, Alo CJ, et al. Increased risk for transverse digital deficiency after chorionic villus sampling: results of the United States Multistate Case-Control Study, 1988–1992. *Teratology*. 1995;51:20–29
19. Mahoney MJ. Limb abnormalities and CVS. *Lancet*. 1991;337:1422–1423
20. Bissonnette JM, Busch WL, Buckmaster JG, Olson SG, Nesler CL. Factors associated with limb abnormalities after chorionic villus sampling. *Prenat Diagn*. 1993;13:1163–1165
21. Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. *N Engl J Med*. 1989;320:19–23
22. Genest DR, Richardson A, Rosenblatt M, Holmes LB. Limb defects and omphalocele in a 17-week fetus following first trimester misoprostol exposure. *Clin Dysmorphol*. 1999;8:53–58
23. Cordero L, Landon MB. Infant of the diabetic mother. *Clin Perinatol*. 1993;20:635–648
24. Light TR, Ogden JA. Congenital constriction band syndrome pathophysiology and treatment. *Yale J Biol Med*. 1993;66:143–155
25. Czeizel AE, Vitez M, Kodaj I, Lenz W. Study of isolated apparent amniogenic limb deficiency in Hungary, 1975–1984. *Am J Med Genet*. 1993;46:372–378
26. Basson CT, Huang T, Lim RC, et al. Different TBX5 interactions in heart and limb defined by Holt-Oram syndrome mutations. *Proc Natl Acad Sci U S A*. 1999;96:2919–2924

Limb Deficiencies in Newborn Infants

Caroline K. McGuirk, Marie-Noel Westgate and Lewis B. Holmes

Pediatrics 2001;108;e64
DOI: 10.1542/peds.108.4.e64

Limb Deficiencies in Newborn Infants

Caroline K. McGuirk, Marie-Noel Westgate and Lewis B. Holmes

Pediatrics 2001;108;e64
DOI: 10.1542/peds.108.4.e64