Published in final edited form as:

Am J Med Genet A. 2008 September 15; 146A(18): 2385–2389. doi:10.1002/ajmg.a.32485.

The Population-Based Prevalence of Achondroplasia and Thanatophoric Dysplasia in Selected Regions of the US

D.K. Waller[1,*], **A. Correa**[2], **Tuan M. Vo**[3], **Y. Wang**[4], **C. Hobbs**[5], **P.H. Langlois**[6], **K. Pearson**[7], **P.A. Romitti**[8], **G.M. Shaw**[9], and **J.T. Hecht**[1]

[1]Houston Health Science Center, The University of Texas, Houston, Texas

[2]Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[3]Department of Obstetrics & Gynecology, University of Medicine and Pharmacy of Ho Chi Minh City, Ho Chi Minh City, Viet Nam

[4]New York State Congenital Malformations Registry, New York State Health Department, Albany, New York

[5]Department of Pediatrics, Birth Defects Research Section, University of Arkansas for Medical Sciences and Arkansas Children's Hospital Research Institute, Little Rock, Arkansas

[6]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas

[7]Oklahoma Birth Defects Registry, Oklahoma State Health Department, Oklahoma City, Oklahoma

[8]Iowa Registry for Congenital and Inherited Disorders, The University of Iowa, Iowa City, Iowa

[9]March of Dimes Birth Defect Foundation/California Department of Health Services, California Birth Defects Monitoring Program, Berkeley, California

Abstract

There have been no large population-based studies of the prevalence of achondroplasia and thanatophroic dysplasia in the United States. This study compared data from seven population-based birth defects monitoring programs in the United States. We also present data on the association between older paternal age and these birth defects, which has been described in earlier studies. The prevalence of achondroplasia ranged from 0.36 to 0.60 per 10,000 livebirths (1/27,780–1/16,670 livebirths). The prevalence of thanato-phoric dysplasia ranged from 0.21 to 0.30 per 10,000 livebirths (1/33,330–1/47,620 livebirths). In Texas, fathers that were 25–29, 30–34, 35–39, and ≥40 years of age had significantly increased rates of de novo achondroplasia among their offspring compared with younger fathers. The adjusted pre-valence odds ratios were 2.8 (95% CI; 1.2, 6.7), 2.8 (95% CI; 1.0, 7.6), 4.9 (95% CI; 1.7, 14.3), and 5.0 (95% CI; 1.5, 16.1),respectively. Using the same age categories, the crude prevalence odds ratios for de novo cases of thanatophoric dysplasia in Texas were 5.8 (95% CI; 1.7, 9.8), 3.9 (95% CI; 1.1, 6.7), 6.1

[*]Correspondence to: Dr. D.K. Waller, The University of Texas at Houston, School of Public Health, 1200 Hermann Pressler Dr, Suite E-619, Houston, TX 77030. kim.waller@uth.tmc.edu.

(95% CI; 1.6, 10.6), and 10.2 (95% CI; 2.6, 17.8), respectively. These data suggest that thanatophoric dysplasia is one-third to one-half as frequent as achondroplasia. The differences in the prevalence of these conditions across monitoring programs were consistent with random fluctuation. Birth defects monitoring programs may be a good source of ascertainment for population-based studies of achondroplasia and thanatophoric dysplasia, provided that diagnoses are confirmed by review of medical records.

Keywords

achondroplasia; thanatophoric dysplasia; prevalence; paternal age; population-based; birth defects monitoring programs

INTRODUCTION

Achondroplasia accounts for more than 90% of disproportionate short stature or dwarfism [Vajo et al., 2000]. It is associated with increased mortality in childhood, obesity and morbidity due to lumbar stenosis, and other nonspecific joint problems [Hecht et al., 1987; Hall, 1988]. Affected individuals have normal intelligence and are able to reproduce. Their mean lifespan has been estimated to be 61 years compared with 71 years for the general population [Hecht et al., 1987]. The phenotype for achondroplasia is distinct from other skeletal dysplasias and can be readily identified by newborn examination and can sometimes be identified by prenatal ultra-sonography. Diagnosis can also be confirmed by radiographs and molecular mutation analysis [Vajo et al., 2000]. Achondroplasia rarely presents as a fetal death and prenatally diagnosed cases are generally recognized late in pregnancy.

Achondroplasia is inherited in an autosomal dominant pattern, and the gene is fully penetrant. Over 90% of cases are sporadic [Vajo et al., 2000] and more than 97% of them are caused by one of two mutations (G1138A and G1138C) in the *FGFR3* gene at chromosome locus 4p16.3 [Vajo et al., 2000]. The specificity of these mutations for achondroplasia has been demonstrated in American, European, Chinese, Japanese, Spanish and Turkish populations [Katsu-mata et al., 2000; Ni et al., 2002; Pehlivan et al., 2003]. One study estimated the recurrence risk of achondroplasia among siblings of an affected individual to be 0.23% (1 recurrence per 443 siblings) [Mettler and Fraser, 2000], suggesting that germline mosaicism does not account for a significant number of cases.

Thanatophoric dysplasia is a relatively common form of dwarfism that often presents as a late fetal death [Karczeski and Cutting, 2004]. Because infants who are born alive with this condition almost invariably die in the first day or two after birth, all cases result from new mutations. There are two distinct phenotypes, thanatophoric dysplasia I and thanatophoric dysplasia II. Thanatophoric dysplasia I is most commonly caused by one of three mutations (R248C, Y373C, and S249C) in the *FGFR3* gene. A single mutation of K650E in the *FGFR3* gene causes all cases of thanatophoric dysplasia II [Karczeski and Cutting, 2004].

The frequency of these disorders is of interest because both conditions are predominately due to de novo or new mutations in the fibroblast growth factor receptor 3 gene *(FGFR3).*

Also, the mutation for achondroplasia has been shown to originate almost exclusively from paternal germ cells [Wilkin et al., 1998; Vajo et al., 2000].

Czeizel suggested that achondroplasia might potentially serve as a sentinel birth defect that could be monitored to detect an increase in the rate of mutations in human populations [Czeizel, 1989]. The purpose of this study is to report the prevalence of achondroplasia and thanatophoric dysplasia ascertained by seven birth defects monitoring programs in the United States. We conducted this investigation to obtain current estimates of the frequency of these conditions and to examine the consistency of these estimates across birth defect monitoring programs.

MATERIALS AND METHODS

The data examined in this study derived from seven state or city programs in the United States: the Arkansas Reproductive Health Monitoring System, the California Birth Defects Monitoring Program, the Metropolitan Atlanta Congenital Defects Program, the Iowa Registry for Congenital and Inherited Disorders, the New York State Congenital Malformations Registry, the Oklahoma Birth Defects Registry, and the Texas Birth Defects Epidemiology and Surveillance Branch.

All of the birth defect monitoring programs in this study base their prevalence rates on cases of birth defects born to mothers who resided in a defined geographic area at the time of the infants birth. All of the programs, except New York and California, ascertained birth defects occurring among livebirths, late fetal deaths (≥20 weeks of gestation) and elective abortions (≥20 weeks of gestation) during the years reported in this study. The New York program ascertained only livebirths. The California program ascertained late fetal deaths and livebirths, but not elective abortions.

With the exception of New York program, each of these programs conducts active surveillance for birth defects. The New York Program uses a combination of active and passive methods for surveillance. All of the active registries employ abstractors who visit birthing and pediatric hospitals in their surveillance area and screen medical records to identify infants with birth defects. Once an infant with a birth defect is identified physicians notes and information on diagnostic procedures are abstracted from the medical record. Each of the registries employed clinical geneticists (Atlanta, Iowa, Texas), pediatricians (Arkansas), or trained specialists (California, New York and Oklahoma) to routinely review information on cases that were suspected to have achondroplasia, thanatophoric dysplasia, other monogenic disorders, syndromes or chromosomal abnormalities. Registry experts confirmed cases of achondroplasia and thanatophoric dysplasia if there were records of a clear diagnosis based on one or more of the following; a molecular mutation analysis, a radiograph or a prenatal ultrasound examination or a physical exam conducted by a clinical geneticist.

We tabulated the data received from each program, calculating prevalence per 10,000 livebirths and 95% confidence intervals, for each condition. In addition, we conducted tests of homogeneity to determine whether differences in the prevalence of these conditions

across monitoring programs were con-sistent with random fluctuation or reflected real differences in rates or ascertainment of these con-ditions. All computations were made using STATA version 8.2.

RESULTS

Table I shows the prevalence of achondroplasia for each of the seven programs that contributed data to the study, with data for the earliest years listed first and data from later years listed last. The prevalence ranged from a low of 0.36 per 10,000 births in New York to a high of 0.60 per 10,000 births in Oklahoma. The chi square test for homogeneity (P = 0.19); indicated that differences in these prevalence rates were consistent with random fluctuation.

Four sites, Atlanta, Iowa, Oklahoma and Texas, contributed prevalence data on thanatophoric dysplasia (Table II). The other three programs did not routinely code cases of thanatophoric dysplasia and thus could not provide data on this condition. The prevalence of thanatophoric dysplasia ranged from a low of 0.21 per 10,000 births in both Texas and Oklahoma to a high of 0.30 per 10,000 births in Iowa. The chi square test for homogeneity was (P = 0.55); again indicating that the differences in the rates across these four states were consistent with random fluctuation.

We were able to obtain more detailed information on diagnostic variables and demographic variables for the Texas cases from the Birth Defects Epidemi-ology and Surveillance Branch of the Texas Depart-ment of State Health Services.

Of the 79 cases of achondroplasia in Texas, one was an elective termination, two were late fetal deaths and 76 were livebirths. Two of the 76 livebirths resulted in neonatal deaths. The clinical information abstracted by the registry indicated that six of the 79 cases of achondroplasia were inherited, that is, had an affected parent. Among the 73 cases that were not inherited; there were 35 males and 38 females. Using data from Texas birth certificates to represent the distribution of father's age among unaffected infants, we examined the association between older paternal age and the prevalence of having an infant with a de novo case of achondro-plasia in Texas between 1996 and 2002. Compared with fathers that were younger than 25 years of age at the time of the infant's birth, fathers that were 25–29, 30–34, 35–39, and ≥40 years of age had significantly increased prevalence rates of infants with thanatophoric dysplasia. The crude prevalence odds ratios for these categories of paternal age were 5.8 (95% CI; 1.7, 9.8), 3.9 (95% CI; 1.1,6.7), 6.1 (95% CI; 1.6, 10.6), and 10.2 (95% CI; 2.6, 17.8), respectively. Due to the small number of cases with this diagnosis, we did not perform multivariate analyses. Older maternal age was not associated with with fathers that were younger than 25 years of age at the time of the infant's birth, fathers that were 25–29, 30–34, 35–39, and ≥40 years of age had significantly increased prevalence rates of infants with achon-droplasia. The adjusted prevalence odds ratios for these categories of paternal age were 2.8 (95% CI; 1.2, 6.7), 2.8 (95% CI; 1.0, 7.6), 4.9 (95% CI; 1.7,14.3), and 5.0 (95% CI; 1.5, 16.1), respectively. These results were independent of father's race, father's educa-tional level and mother's age. Older maternal age was not associated with achondroplasia independently of older paternal age.

Of the 43 thanatophoric dysplasia cases in Texas, five (11.6%) presented as fetal deaths and nine (20.9%) were elective terminations. Of the 29 cases that were born alive, medical records indicated that 28 died during the neonatal period. Clinical information abstracted by the Texas registry indicated that none of the cases of thanatophoric dysplasia were inherited. There were 26 males and 17 females. We also examined the association between older paternal age and the prevalence of having an infant with thanatophoric dysplasia in Texas between 1996 and 2002. Compared with fathers that were younger than 25 years of age at the time of the infant's birth, fathers that were 25–29, 30–34, 35–39, and ≥40 years of age had significantly increased prevalence rates of infants with thanatophoric dysplasia. The crude prevalence odds ratios for these categories of paternal age were 5.8 (95% CI; 1.7, 9.8), 3.9 (95% CI; 1.1, 6.7), 6.1 (95% CI; 1.6, 10.6), and 10.2 (95% CI; 2.6, 17.8), respectively. Due to the small number of cases with this diagnosis, we did not perform multivariate analyses. Older maternal age was not associated with thanatophoric dysplasia.

In Texas, the physician notes that were abstracted by the registry for all fetuses or infants classified as having achondroplasia or thanatophoric dysplasia indicated that in all cases the diagnosis was confirmed by X-ray or prenatal ultrasound examina-tion. Only, three of the cases of achondroplasia and none of the cases of thanatophoric dysplasia in Texas were noted to have been confirmed by molecular mutation analysis.

DISCUSSION

Seven previous studies have reported estimates for the prevalence of achondroplasia. Four of these studies were population-based [Oberklaid et al., 1979; Andersen and Hauge, 1989; Stoll et al., 1989; Kallen et al., 1993] and three were hospital-based [Orioli et al., 1986; Camera and Mastroiacovo, 1988; Rasmussen et al., 1996]. The population-based studies covered birth populations of 77,977 [Ander-sen and Hauge, 1989], 105,374 [Stoll et al., 1989], 492,889 [Oberklaid et al., 1979], and 9,500,000 [Kallen et al., 1993]. And, the hospital-based studies covered birth populations of 126,316 [Rasmussen et al., 1996], 349,470 [Orioli et al., 1986], and 838,717 [Camera and Mastroiacovo, 1988]. The population-based studies reported prevalences of achondroplasia of 0.13 [Andersen and Hauge, 1989], 0.28 [Kallen et al., 1993], 0.39 [Oberklaid et al., 1979], and 0.64 [Stoll et al., 1989] per 10,000 births. The hospital-based studies reported prevalences of 0.24 [Rasmussen et al., 1996], 0.37 [Camera and Mastroiacovo, 1988] and 0.46 [Orioli et al., 1986] per 10,000 births. In comparison, we report data from birth populations ranging from 250,000 to 3,500,000 across seven sites. The prevalences of achondroplasia that we observed across seven birth defects monitoring programs ranged from 0.36 to 0.60 per 10,000 livebirths and were consistent with those of previous studies.

Three of the population-based studies described previously reported prevalences for thanatophoric dysplasia of 0.17 [Kallen et al., 1993], 0.28 [Stoll et al., 1989], and 0.38 [Andersen and Hauge, 1989] per 10,000 births. Three hospital-based studies described previously reported prevalences of 0.09 [Orioli et al., 1986], 0.35 [Camera and Mastroiacovo, 1988], and 0.40 [Rasmussen et al., 1996] per 10,000 livebirths. The prevalence rates from the four birth defects monitoring programs reported in the current

study are similar to those reported by previous studies, although their range is narrower, that is, 0.21–0.30 per 10,000 livebirths.

Rates of thanatophoric dysplasia were similar across four state monitoring programs. Based on these monitoring programs, thanatophoric dysplasia is one-third to one-half as frequent as achondropla-sia. Each of the four states that reported rates of thanatophoric dysplasia for this study ascertained cases of birth defects that presented as livebirths, fetal deaths or elective abortions. There was no change in the prevalence rates among states that reported data from earlier time periods compared to those reporting data from later time periods. In Texas virtually all cases of thanatophoric dysplasia were elective abortions, fetal deaths or early neonatal deaths as expected for a lethal condition. The observation that, in Texas, 9 of 43 cases or 20.9% of cases were elective abortions is consistent with the high frequency of elective abortions that has been observed for other lethal birth defects in Texas [Waller et al., 2000].

Differences in the rates of achondroplasia across the seven monitoring programs were not correlated with the time periods for which surveillance data were available. The lowest prevalence rate of 0.36 per 10,000 births was reported by New York which is the only monitoring program of the seven that does not ascertain birth defects occurring among fetal deaths and elective abortions. However, Atlanta and Texas both reported rates of 0.39 per 10,000; nearly as low as the rate reported by New York.

The observation that most of the infants with achondroplasia in the Texas data survived the neonatal period is consistent with expectations for this disease and suggests that in the Texas registry cases of achondroplasia are not greatly misclassified with thanatophoric dysplasia or other lethal skeletal dysplasias. Nonetheless, out of 79 infants with achondroplasia, there were two neonatal deaths and two fetal deaths, representing a higher rate of perinatal death than would be expected based on the limited data that are available regarding perinatal mortality among infants with achondroplasia [Hecht et al., 1987]. We cannot exclude the possibility that some or all of these four perinatal deaths represent cases of thanatophoric dysplasia or other lethal skeletal dysplasias that were mistakenly classified as achondroplasia.

To date, there has been little effort to study environmental risk factors that might be associated with an increased risk of having an infant with achondroplasia or thanatophoric dysplasia. A single study by Czeizel [1989] reported no detectable increase in these and similar conditions following the Chernobyl accident. Agents that cause mutations in paternal germ cells such as radiation, chemo-therapy or other mutagenic chemicals could potentially be risk factors for these conditions. Genetic variants that adversely affect DNA repair mecha-isms or low levels of dietary anti-oxidants that protect against free radicals might also be potential risk factors.

Achondroplasia and thanatophoric dysplasia result from substitution mutations in the *FGFR3* gene, which arise due to copy errors during mitosis. Substitution mutations in paternal germ cells could occur at any point during fetal life, childhood, or adult male life. If they occur in stem cells, they can persist indefinitely. Goriely et al. [2005] suggested that the

mutation that causes achondroplasia might occur in stem cells relatively early during the father's life, and that cells with this mutation might exhibit a survival advantage, leading to clonal expansion. Thus, any study of paternal risk factors for fetuses and infants affected by achondroplasia or thanatophoric dysplasia would need to consider a wide exposure window for the timing of paternal exposures.

We have observed that the rates of achondroplasia and thanatophoric dysplasia measured by seven different birth defects monitoring programs are similar to the rates reported by earlier studies. In Texas, we confirmed the strong association between older paternal age and these birth defects that has been reported by previous studies [Stoll et al., 1982; Lian et al., 1986]. This suggests that birth defects monitoring programs might be an acceptable source of ascertainment of cases of achondroplasia and thanatophoric dwarfism. However, if cases are obtained from birth defects monitoring programs, medical records or genetic testing should be used to confirm diagnoses, as some misclassification could be present with these rare disorders.

ACKNOWLEDGMENTS

This study was supported in part through the cooperative agreement U50/CCU613232 from the Centers for Disease Control and Prevention to the Texas Department of State Health Services Center for Birth Defects Research and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Centers for Disease Control and Prevention.

Grant sponsor: Centers for Disease Control and Prevention; Grant number: U50/CCU613232.

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Table I.

Achondroplasia: Prevalence per 10,000 Births Across Seven U.S. Monitoring Programs

Program	Type	Years	Cases	Births	Rate	95% CI
Atlanta	A	68–01	44	1,129,972	0.39	0.30, 0.48
California	A	83–97	168	3,572,233	0.47	0.42, 0.52
Iowa	A	83–01	30	733,196	0.41	0.30, 0.52
New York	A/P	92–01	96	2,664,131	0.36	0.30, 0.43
Arkansas	A	93–99	13	250,000	0.52	0.32, 0.72
Oklahoma	A	94–03	29	484,013	0.60	0.46, 0.74
Texas	A	96–02	79	2,042,554	0.39	0.30, 0.47

A, active; P, passive; CI, confidence interval. Chi square test for homogeneity, *P* value = 0.19.

Table II.

Thanatophoric Dysplasia: Prevalence per 10,000 Births Across Four U.S. Monitoring Programs

Program	Type	Years	Cases	Births	Rate	95% CI
Atlanta	A	68–01	28	1,129,972	0.25	0.17, 0.33
Iowa	A	83–01	22	733,196	0.30	0.20, 0.41
Oklahoma	A	94–03	10	484,013	0.21	0.09, 0.32
Texas	A	96–02	43	2,042,554	0.21	0.14, 0.26

A, active; Chi Square test for homogeneity, *P* value = 0.55.