

Mortality in Babies with Achondroplasia: Revisited

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BACKGROUND: Natural history studies performed 30 years ago identifying higher mortality among children born with achondroplasia, a genetic dwarfing condition, resulted in clinical recommendations aimed at improving mortality in childhood. The objective of this study was to determine if mortality rates have changed over the past few decades. **METHODS:** Children born with achondroplasia during 1996 to 2003 were ascertained from the Texas Birth Defects Registry and matched with death certificate data from the Bureau of Vital Statistics through 2007. Infant and overall mortality rates, both crude and standardized to the 2005 (SMR₂₀₀₅) and 1975 (SMR₁₉₇₅) U.S. populations, were calculated. **RESULTS:** 106 children born with achondroplasia were identified. Four deaths were reported, with all occurring in the first year of life (mortality rate: 41.4 /1000 live-births). Infant mortality was higher when standardized to the 2005 U.S. population (SMR₂₀₀₅:6.02, 95% CI:1.64–15.42) than the 1975 population (SMR₁₉₇₅:2.58, 95% CI:0.70–6.61). **CONCLUSION:**

The higher SMR₂₀₀₅ compared with SMR₁₉₇₅, along with the fact that SMR₁₉₇₅ was nearly half that of a previous cohort reported 25 years ago (rate ratio: 0.53, 95% CI: 0.11–2.25), reflect a discrepancy in the changes in mortality in the overall population and in our cohort. Although an overall improvement in mortality, especially after the first year of life, is observed in our cohort, children with achondroplasia are still at a much higher risk of death compared with the general population. A longer follow-up is needed to elucidate whether evaluation/intervention changes have resulted in significant improvement in long-term survival among these patients.

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Introduction

Achondroplasia is a well-characterized genetic dwarfing condition caused by mutation in fibroblast growth factor receptor-3 and characterized by short long bones, midface hypoplasia with frontal bossing, short broad hands with a trident finger configuration, macrocephaly, short vertebral pedicles, hypoplastic foramen magnum and a small skull base (Horton et al., 2007; Wynn et al., 2007). It is the most common skeletal dysplasia with a birth prevalence of 1/26,000 (Oberklaid et al., 1979; Hunter et al., 1998; Waller et al., 2008). Natural history studies have defined numerous complications including: delayed motor development, hypotonia, recurrent otitis media, bowed legs, sleep apnea, and sudden death (Hecht and Butler, 1990; Hunter et al., 1998; Wynn et al., 2007). Apnea and sudden death in achondroplastic babies from foramen magnum compression are the most severe complications (Yang et al., 1977; Pauli et al., 1984; Hecht et al., 1987; Horton et al., 2007). Case reports suggested that sudden death was increased in achon-

droplasia and a historical cohort study in 1987 of 701 individuals with achondroplasia confirmed a high risk of sudden death of 7.5% in babies less than 1 year of age and 2.5% risk of sudden death in children between 1 and 4 years of age (Pauli et al., 1984; Hecht et al., 1987). These were ultimately found to be the result of foramen magnum stenosis (Yang et al., 1977; Pauli et al., 1984; Hecht et al., 1987). This led to an increased clinical awareness of risk factors and subsequent recommendations for evaluation and surgical intervention of achondroplasia babies and children (Bland and Emery, 1982; Pauli et al., 1984; Keiper et al., 1999; Ain et al., 2000; Horton et al., 2007; Wynn et al., 2007).

Long-term follow-up of the original 1987 cohort demonstrated that the increased mortality persisted through adulthood and average life expectancy was decreased by 10 years (Wynn et al., 2007); however, there have been no studies to assess if the evaluation and intervention recommendations suggested over the past two decades have resulted in a change in mortality among achondroplastic children born since then. Insufficient data have prevented a comparison of mortality rates in children born over the past decade in comparison to the older studies. The purpose of the current study was to determine the crude mortality rate and standardized mortality ratios (SMRs) in children with achondroplasia born in Texas from 1996 through 2005.

Materials and Methods

All children born between 1996 and 2005 in Texas and diagnosed with achondroplastic dwarfism (BPA code 756.430) were identified through the Texas Birth Defect's Registry, which is part of Birth Defects Epidemiology and Surveillance Branch (BDESB) of the Texas Department of State Health Services. Registry data is obtained through active surveillance to identify all children born with a birth defect in Texas and contains information on all births from (1) mothers residing

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in the state of Texas, (2) from infants who are born with specific birth defects either diagnosed prenatally or within the first year of life and (3) all pregnancy outcomes (live births, spontaneous fetal deaths, and elective pregnancy termination) (TxDSHS, 2004; Vendola et al., 2009). All records were reviewed by two authors (J.T.H. and S.A.) and babies and children with inconsistent clinical findings were excluded. Only children with a diagnosis of achondroplasia were included in the analysis. All individuals in the cohort were cross-referenced with death certificate data from the Texas Bureau of Vital Statistics through December 31, 2007 to determine the number that died during this time period.

The data from the cohort was then stratified into three different age groups, <1 year of age, 1 to 4 years of age, and 5 to 9 years of age. Age adjusted mortality rates standardized to the 2005 U.S. population were calculated. To facilitate comparison with the 1987 study by Hecht, et al. that reported SMRs for achondroplastic infants and children in Texas from 1960 to 1985, mortality rates standardized to the 1975 U.S. population (used by Hecht et al., 1987) were also calculated.

Results

A cohort of 114 infants with a presumptive diagnosis of achondroplasia was identified in the birth defects registry. After review, eight infants were excluded; six because the diagnostic criteria did not match achondroplasia. One infant was a double dominant combination of spondyloepiphyseal dysplasia and achondroplasia as both parents had these diagnoses, respectively. In addition, one infant had double dominant achondroplasia, which is associated with fetal demise or death in infancy (Pauli et al., 1984).

Of the remaining 106 infants, 53 were males and 53 females. Four deaths (mortality rate of 0.38 per 1000 live births) were identified and verified. Two of these deaths were in male patients. These deaths occurred in the first year of life on days of life 1, 5, 21, and 163. Combined, the 106 infants contributed 96.7 person years for analyses pertaining to the first year of life resulting in 4.14 deaths per 100 person-years. Based on 2005 population mortality rates (Kung et al., 2008), the SMR for the first year of life was 6.02 (95% CI: 1.64–15.42) (Table 1). Based on the 1975 population mortality rates, the SMR for our cohort was 2.58 (95% CI: 0.70–6.61) for the first year. In our cohort, no deaths were identified in children with achondroplasia from 1 through 9 years of age, with all deaths occurring in the first year of life.

Discussion

The results of this population-based study provide evidence that although children born with achondroplasia still have a higher likelihood of death during the first year of life, the infant mortality rate in this population has slightly improved over the past 30 years. This improvement was evident when mortality rates in our cohort were

TABLE 1. Standardized Infant Mortality Rates among Children Born with Achondroplasia in Texas, 1996 to 2005 (Present Cohort) and in a Previously Reported Historical Cohort^a

Cohort ^b	SMR (95% CI)	Rate ratio (95% CI)
Present cohort, SMR-2005	6.02 (1.64–15.42)	–
Present cohort, SMR-1975	2.58 (0.70–6.61)	0.53 (0.11–2.25)
Historical cohort, SMR-1975	4.84 (1.78–10.54)	

^aHistorical cohort reported in Hecht et al, 1997.

^bSMR-2005 = mortality rate standardized to 2005 U.S. population mortality rate; SMR-1975 = mortality rate standardized to 1975 U.S. population mortality rate.

SMR, standardized mortality rates; CI, confidence interval.

compared with mortality rates described in previously published literature.

We had previously described a cohort of children with achondroplasia with an infant mortality rate of 77.6 per 1000 live births (Hecht et al., 1987). This was nearly 5 times higher than the 1975 population infant mortality rate of 16.03 per 1000 live births (<http://www.cdc.gov/nchs/data/dvs/mx196878.pdf>) (SMR: 4.84; 95% CI: 1.78–10.54). As a result of the publication of that report and others that provided evidence for possible causes that contributed to the high mortality, numerous recommendations were suggested for the management and care of children with achondroplasia. The main aim of those recommendations was to increase awareness, early diagnosis, and timely management of potentially fatal co-morbidities in patients with achondroplasia and thus reduce mortality.

The infant mortality rate of 41.4 per 1,000 live births within our present cohort was slightly less than half the rate in our previous study. When both mortality rates were standardized to the 1975 U.S. population for an unbiased comparison, the SMR for the present study (2.58) was nearly half the SMR (4.84) for the previous study. However, this difference was not significant (rate ratio: 0.53; 95% CI: 0.11–2.25). Failure to observe a significant difference may be attributed to the overall reduction in infant mortality over the past few decades. Infant (<1 year) mortality rates for the general population have steadily declined in the past 30 years from 16.03 in 1975 to 6.87 per 1000 live births in 2005. Similarly, mortality among children aged 1 through 4 has also declined in the same period from 69.9 to 29.4 deaths per 100,000 children (Singh and Yu, 1995; Kung et al., 2008).

Given this baseline decrease in mortality, the estimated infant mortality rate in our cohort should have been around 32.6 per 1000 live births. This is comparable to, but lower than, the mortality rate of 41.4 per 1000 live births that we report for our present cohort. It is likely that the small sample size (and the even smaller number of deaths in our sample) may have resulted in insufficient power to provide

statistical evidence for the nearly 50% drop in mortality between the two achondroplasia cohorts. Evidence to support our assumption that there is a real drop in infant mortality (independent of any background population-level improvement in infant survival) is present in the lack of deaths in our cohort that was followed for more than one year. Although we had 93 individuals (aged less than 10 years) contributing a total of 388 person-years beyond the first year of life, no deaths were observed. In comparison, Hecht et al. (1987) reported at least 3 deaths among 120 children that were aged 1 through 4 when joining that study cohort. However, it is possible that given a larger sample size and a longer follow-up period, we would have identified deaths after infancy.

Of interest, the infant mortality rate in our cohort was nearly 6 times higher than infant mortality in the general population in 2005 (SMR: 5.97; 95% CI: 1.63–15.30). This SMR along with the results discussed above suggests that although survival has possibly improved for children born with achondroplasia, this improvement has not been at the same pace as improvement in survival in the general population. Therefore, although improvements in health-care techniques and availability may have contributed to improved survival to some degree in the study population, children with achondroplasia are still at a much higher risk of death compared with the general population.

These results suggest that, at least in Texas, the mortality rate for achondroplastic children older than one year has decreased, suggesting that surveillance recommendations are positively impacting survival. Three of the four deaths in our cohort occurred in the neonatal period suggesting that monitoring of infants with achondroplasia is either not being performed early enough among at-risk infants or that these deaths were in high-risk neonates. If the latter is true, then this may reflect an improvement in survival in most achondroplastic infants while, unfortunately, death may still be unavoidable for those with severe disease or those at a high risk of co-morbidity and mortality despite improved surveillance and neonatal management, namely, these are infants that would have died early historically and in the present cohort. Unfortunately, we did not have data on the exact cause of death and as such cannot determine exactly what, if any, difference in management (e.g., improved monitoring to capture apneic episodes in neonates with achondroplasia) would have prevented the deaths.

These findings underscore the need for continued awareness among healthcare providers of risks associated with achondroplasia and early surveillance among that patient population. A more extensive study with a larger cohort and longer follow-up period is necessary to determine with more certainty the impact of health care changes on mortality and whether these changes have translated into improved long-term survival among children born with achondroplasia.

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References

- Ain MC, Elmaci I, Hurko O, et al. 2000. Reoperation for spinal stenosis in achondroplasia. *J Spinal Disord* 13:168–173.
- Bland JD, Emery JL. 1982. Unexpected death of children with achondroplasia after the perinatal period. *Dev Med Child Neurol* 24:489–492.
- Hecht JT, Butler IJ. 1990. Neurologic morbidity associated with achondroplasia. *J Child Neurol* 5:84–97.
- Hecht JT, Francomano CA, Horton WA, Annegers JF. 1987. Mortality in achondroplasia. *Am J Hum Genet* 41:454–464.
- Horton WA, Hall JG, Hecht JT. 2007. Achondroplasia. *Lancet* 370:162–172.
- Hunter AG, Bankier A, Rogers JG, et al. 1998. Medical complications of achondroplasia: a multicentre patient review. *J Med Genet* 35:705–712.
- Keiper GL Jr, Koch B, Crone KR. 1999. Achondroplasia and cervicomedullary compression: prospective evaluation and surgical treatment. *Pediatr Neurosurg* 31:78–83.
- Kung HC, Hoyert DL, Xu J, Murphy SL. 2008. Deaths: final data for 2005. *Natl Vital Stat Rep* 56:1–120.
- Oberklaid F, Danks DM, Jensen F, et al. 1979. Achondroplasia and hypochondroplasia. Comments on frequency, mutation rate, and radiological features in skull and spine. *J Med Genet* 16:140–146.
- Pauli RM, Scott CI, Wassman ER Jr, et al. 1984. Apnea and sudden unexpected death in infants with achondroplasia. *J Pediatr* 104:342–348.
- Singh GK, Yu SM. 1995. Infant mortality in the United States: trends, differentials, and projections, 1950 through 2010. *Am J Public Health* 85:957–964.
- TxDSSH. 2004. Report of Birth Defects Among 1999–2001 Deliveries. Austin: Texas Department of State Health Services.
- Vendola C, Canfield M, Daiger SP, et al. 2009. Survival of Texas infants born with trisomies 21, 18, and 13. *Am J Med Genet A* 152A:360–366.
- Waller DK, Correa A, Vo TM, et al. 2008. The population-based prevalence of achondroplasia and thanatophoric dysplasia in selected regions of the US. *Am J Med Genet A* 146A:2385–2389.
- Wynn J, King TM, Gambello MJ, Waller DK, Hecht JT. 2007. Mortality in achondroplasia study: a 42-year follow-up. *Am J Med Genet A* 143A:2502–2511.
- Yang SS, Corbett DP, Brough AJ, Heidelberger KP, Bernstein J. 1977. Upper cervical myelopathy in achondroplasia. *Am J Clin Pathol* 68:68–72.