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KAWASAKI SYNDROME IN TEXAS

ABSTRACT

The purpose of this study was to examine the hospitalization rates of Kawasaki Syndrome (KS) among children living in Texas to isolate clusters, identify demographic disparities, and suggest possible causative factors. A retrospective cross-sectional study design identified 330 KS cases from 2,818,460 hospital discharges extracted from the 2004 Texas hospital discharge database. Categorical variables and proportions were analyzed using Pearson Chi-Square analysis for bivariate comparison of hospitalization rates and other demographic and geographic variables. Overall, the majority of the cases (61.5%) fell within the 1 to 4 year age category, representing the highest hospitalization rate at 14.3 per 100,000 children. Almost 75% of the KS population was less than five years old with a hospitalization rate that was about eight times higher than all other children ($p<0.05$). The KS diagnosis occurred for only 49.4% of all KS cases upon admission. About 52% of Non Hispanic Blacks (NHB) used the ER as their main source of admission and Medicaid was the main payment source for Hispanics (67.2%). High density clusters were identified in major metropolitan areas, with the Dallas-Fort Worth and Houston areas representing 26.6% and 18.8% of all of the state's 2004 KS cases, respectively. Although the overall hospitalization rate of KS in Texas is consistent with national rates, significant high risk areas exist, both geographically and demographically. The highest hospitalization rate of KS was found among Asian and Pacific Islanders and NHB children which suggest genetic predisposition for the first group and reflect difficulties with access to healthcare for NHB. With an initial diagnosis rate of less than 50%, educating physicians and other healthcare providers to recognize of the symptoms of KS is imperative,

particularly for ER and primary care providers. Support is recommended mandating KS as reportable condition by hospitals.

Key Words: Kawasaki; children; THCIC; minority; healthcare disparity; Texas.

INTRODUCTION

Kawasaki Syndrome (KS) is a disease that involves the skin, mouth, and lymph nodes typically affecting children under five years of age (American Heart Association [AHA] 2001; Centers for Disease Control [CDC] 2007;Kawasaki Disease Foundation 2007) . It is currently one of the leading causes of acquired cardiovascular disease in children in the U.S. (AHA 2001; CDC 2007; Kawasaki Disease Foundation 2007). KS was first described in Japan by Kawasaki in 1967 (Kawasaki, Kosaki, Okawa, Shigematsu, and Yanagawa 1974). The first cases reported beyond Japan's islands occurred in Hawaii and reported in 1976 (Melish, Hicks, and Larson 1976).

We defined KS according to Centers for Disease Control (CDC 2007) and American Heart Association (AHA 2001) criteria. These diagnostic criteria include presence of a high fever for four or five days duration along with four or more additional symptoms. The additional clinical signs include rash, red eyes, red swollen and cracked lips, "strawberry" tongue, swollen hands and feet, swollen lymph nodes, or redness of the palms of the hands and of the soles of the feet (AHA 2001).For epidemiologic surveillance, CDC (2007) defines KS as a patient demonstrating fever for five or more days or until the date of administration of intravenous immunoglobulin, if given before day five of fever, and the presence of at least four of the clinical signs of rash, cervical lymphadenopathy at least 1.5 cm in diameter, bilateral conjunctival injection, oral mucosal changes, and peripheral extremity changes.

When the fever is misinterpreted and the rash is overlooked by physicians, KS can progress untreated. Cardiac involvement of an untreated KS child can have serious and sometimes fatal consequences (Newburger et al. 2004). The main complication for those surviving KS is Coronary Artery Aneurysms (CAA); (Freeman and Shulman 2006). CAA has an 8.6% incidence in patients meeting the diagnostic criteria for KS and a 25% incidence in those not receiving a timely KS diagnosis (Freeman and Shulman 2006).

Treatment within ten days after onset of fever is essential to decrease the risk of heart problems. With appropriate detection and treatment, the incidence of CAA can be reduced to from 1% to 5% (Gersony 1991). Treating KS consists of administering intravenous immunoglobulin (IVG) for 8 to 12 hours within ten days of fever onset. High doses of aspirin are administered until the fever subsides. A decreased dosage of aspirin continues for at least two months to reduce spontaneous coronary thrombosis (Rauch 1987).

The etiology of KS is unknown. Possible causes are prior respiratory disease, exposure to carpet cleaning chemicals, use of humidifiers, or living in close proximity to bodies of water (Rauch et al. 1988; Rauch et al. 1991; Lloyd et al. 2001; Kawasaki Disease Foundation 2007). Other researchers strongly have suggested an infectious cause (Rauch 1987; Gersony 1991; Belay et al. 2005 ;). Several microbial agents, such as rickettsiae, propionibacterium acnes, klebsiella pneumoniae, ehrlichia sp, parainfluenza virus types 2 and 3, Epstein- Barr virus, rotavirus, and many others, have been studied in KS patients (Rauch et al. 1991; Chua 2001; Belay et al. 2005; Dominguez et al. 2006). Although multiple infectious agents and toxins have been implicated in the etiology of the disease, none have been confirmed to cause KS (Chang 2003; Burns 2007). With the etiology of KS unknown after 40 years of intense research (Kao 2005), no specific laboratory test, such as blood test or throat culture, has been

developed to diagnose KS and atypical cases (CDC 2007). Delayed diagnosis and treatment have been unavoidable. Furthermore, diagnosis is complicated by KS' symptoms and signs being present in other illnesses (Gersony 1991).

Estimation of national and state incidence of KS has been difficult, because case reporting to the CDC has been sporadic (Kao 2005). Tracking has been left to state agencies (Holman et al. 2003). As is the case with any large passive surveillance system, only a fraction of the total cases have been reported (Rauch et al. 1991).

Outbreaks of KS have been reported, but active reporting is only performed in 11 states (Holman et al. 2003). Instead, studies using hospital discharge data have been used for KS surveillance and reporting (Chang 2003). In outbreak investigations conducted in Texas and North Carolina in 1984, and in Colorado in 1986, the CDC found KS patients' homes tended to be less than 200 yards from the nearest body of water, usually a creek or drainage ditch (Rauch et al. 1988). Additionally, Chang found the overwhelming majority of children with KS (>96%) are hospitalized (Burns et al. 1984). In the U.S. in 2005, the estimated number of new KS cases totaled 5,000, and the attack rate for children under five years of age was 20 to 25 cases per 100, 000 children (Chang 2003). In Texas, the current incidence of KS and CAA resulting from KS is not known, because KS is not actively tracked by the Texas Department of State Health Services (Su 2007).

Kawasaki Syndrome is most common among children of Japanese and Korean descent but can affect all ethnic and racial groups (Belay et al. 2006). Evidence indicates a higher rate of KS among Asian Americans and Pacific Islanders (32.5 cases per 100,000 children less than five years old). The rates are less for Non-Hispanic Blacks (16.9 cases per 100,000 children less than five years old) and Hispanics (11.1 cases per 100,000 children less than five

years old). The lowest rate was among Non-Hispanic Whites (9.1 cases per 100,000 children less than five years old (Newburger et al. 2004). For the Hispanic group, treatment for the CAA outcome of KS has been reported as being delayed due to the group's lack of access to healthcare (Belay et al. 2006).

The purpose of the present study was to describe the hospitalization rate of KS in Texas children using the Texas hospital discharge database and to describe the demographic characteristics of Texas children with KS.

METHODOLOGY

This retrospective cross-sectional study employed data from a public domain data file maintained by the Texas Health Information Council (THCIC), the Texas warehouse of hospital discharge data (Texas Department of Health Services 2004). Data were extracted from a base population of 2,818,460 hospital discharges obtained from the 2004 public THCIC dataset. Cases with KS were identified using the International Classification of Diseases, 9th revision Clinical Modification (ICD-9 CM) code: 446.1 for Kawasaki Syndrome or mucocutaneous lymph node syndrome present in the principal discharge diagnosis and all other discharge diagnoses (U.S. Department of Health and Human Services 1988; Texas State Data Center 2005).

Characteristics of Interest

Age, gender, race/ethnicity, risk mortality, illness severity, admitting diagnosis, source of admission, and payment source were investigated. The six age categories were,

respectively, less than 1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, 15 to 17 years, and 18 years or older. For specific comparisons, these categories were dichotomized into less than five years old and equal or greater than five years old. Race and ethnicity were restructured to four major groups of Non-Hispanic Whites (NHW), Non-Hispanic Blacks (NHB), Hispanics, and Asians and Pacific Islanders (API). Other admitting diagnosis in KS patients included: fever (ICD9 code 780.6), and rash (ICD9 code 782.1). All other admitting diagnoses were combined and placed in the category labeled as Other with their frequencies less than five percent. Principal diagnosis was identified in the same way in terms of ICD 9th CM. Admission sources included Emergency Room (ER), physician referral, transfer from other hospital, or other. Risk of mortality score and severity of illness was assigned from All Patient Refined Diagnosis Related Group (APR-DRG) from the 3M APR-DRG Grouper, version 20, indicating the likelihood of dying and the extent of physiologic decompensation. The four insurance status groups were private insurance, Medicaid, uninsured (self pay or indigent), and Other-labeled insurance. The Texas counties with more than four percent of the state's KS admissions are reported in Table 3.

Data Analysis

Categorical variables and proportions were analyzed using Pearson Chi -Square analysis for bivariate comparison by ethnicity, gender, and other variables. Hospitalization rates (Chang 2003) were calculated with the number of cases as numerator and the population estimate for 2004 by age as denominator (proxy for incidence rate). The population estimate for 2004 by age and county were obtained from the Texas State Data Center and Office of the State Demographer (Texas State Data Center 2005). A *p*-value of less than 0.05 was

considered statistically significant. Statistical analyses were performed using SPSS version 15. For this study's protocol, appropriate approvals related to the protection of human subjects were sought and received from the Institutional Review Board of the University of North Texas Health Science Center at Fort Worth.

RESULTS

Patient Characteristics

The discharge diagnosis consistent with KS was identified for a total of 330 cases. Sixty percent were male, 5.7 % API, 37.9% Hispanic, 31.9% NHW and 17.6% NHB. The stratified age distribution for the 330 KS cases is shown in Table 1. The majority of the cases at 61.5% fell in the 1 to 4 years of age category. This age category represented the highest hospitalization rate at 14.3 per 100,000 children. Almost 75% of the KS population was less than five years old, and its hospitalization rate was about eight times higher than greater or equal than five years old (13.8 per 100,000 children versus 1.8 per 100,000 children, respectively), which was significant ($p<0.05$, Table1). For the category with age less than one year old, the highest hospitalization rate for API was 44.9 per 100,000, while NHW displayed 8.8 per 100,000 children and NHB and Hispanics exhibited 14.7 and 12.5 per 100,000 children, respectively ($p< 0.05$).

As seen in Table 1 with hospitalization rates by race/ethnicity for those less than five years old, the highest hospitalization rate occurred for API and NHB with 29.8 and 18.4 per 100,000 children respectively, as compared to NHW representing 9.7 per 100,000 children ($p< 0.05$). In both age groups, NHB presented significantly higher hospitalization rates than NHW, the control group. In comparing age group by gender, males' less than one year old category, were diagnosed with KS at twice as often as females of the same age and demonstrated

significant higher hospitalization rates ($p < 0.05$), (Table 1). Anecdotally, only two cases of KS with CAA were reported.

Table 1 about here

Table 2 presents the results of risk mortality, illness severity, admitting diagnosis, source of admission, and payment source by ethnicity for the 330 KS cases. Regarding admitting diagnoses, KS was diagnosed as such only 49.4% of the time upon admission to the hospital and only 22.2% in the API group. Fever was the second most frequent admitting diagnosis at 32.4% and occurred at a 72.2% rate for the API group. Rash and non specific eruption were present in 5.8% of the cases and was higher for NHW (9.5%; Table 2). There were 41cases with all other admitting diagnoses constituting 12% of all cases. The variable, Physician referral was the source of admission for 48.8% of the cases followed by ER admission for 39.7%. Non Hispanic blacks' use of the ER was 51.7% as compared to 33.3% for NHW. Non Hispanic blacks had a much lower private insurance rate (36.2 %) than NHW (53.3%; Table 2). Hispanics used Medicaid as their primary payment source (67.2%) more than three times as often as NHW (20 %).

Table 2 about here

Table 3 depicts the Texas counties representing at least 4% of the 2004 KS cases. Collin County had the highest incidence rate of KS in the Texas Counties with a rate of 29.0 per 100,000 for children less than five years old and 30.6 per 100,000 for children of age less than 1 year old. Travis County presented a high hospitalization rate with 42 per 100,000 children of age less than one year old. Harris County, which includes Houston, reported the most KS cases in the state; Dallas County reported the second highest number of cases. The

two counties' hospitalization rates were 15.7 and 16.1 per 100,000 cases, respectively, in children of age less than five years old. Travis County, home to Austin, and Bexar County, home to San Antonio, showed similar frequencies of KS cases but hospitalization rates of 17.6 and 11.7 per 100,000 children less than five years old, respectively (Table 3). Three of the highest hospitalization rates by county (Collin, Dallas, and Tarrant) occurred for the Dallas Fort Worth Metroplex (DFW) area, representing 21.5% of the state's 2004 KS cases. By including the remaining DFW counties, all of DFW represented 26.6% of the state's 2004 KS cases. The counties not listed in Table 3, because their frequencies less than 4%, were combined and placed in the category labeled as other. Consequently, 147 KS cases in the other-labeled counties represented 44.6% of the state's 2004 KS cases.

Table 3 about here

DISCUSSION

All ethnic/racial groups were affected by KS in the study sample, with the highest hospitalization within API for the less than five years old group at 29.8 per 100,000 children. This figure is close to the 32.5 per 100,000 children reported by Newburger et al. (2004) and to other academic evidence indicating a higher hospitalization rate of KS among API children (Burns 2007; Burns et al. 1984; Chang 2003; Gersony 1991; Holman et al. 2003; Kao 2005).We concur with the former study for all other racial/ethnic patients of age less than five years old, based on our finding of a higher rate of 18.4 per 100,000 children for NHB and of a lower rate for Hispanic and NHW of 12.6 and 9.7 per 100,000 children, respectively. We find this pattern to be similar to that of children of age less than one year old. However, API's KS hospitalization rate was 44.9 per 100,000 children. For children of all ethnicities and races with age less than five years old, the estimated 2004 KS hospitalization rate was 13.8 per

100,000 children. This estimated KS rate was consistent with KS hospitalization rates reported in previous studies within the US (range of 9–19 per 100,000 children); Burns 2007; CDC 2007; Chang 2003). Male children were more likely than female children in both of the age categories of less than 1 year old and 1 to 4 years old to be diagnosed with KS, a finding which corresponds with the academic evidence (Burns et al. 1984; Gersony 1991; Chang 2003; Holman et al. 2003; Newburger et al. 2004; Kao 2005; Burns 2007;).

Texas has an access to care crisis that disproportionately and adversely affects minorities' children (Angel, Lein and Henrici 2006). Results of this study suggest that for the Hispanic population, the most frequent source of admission came from physician referrals (45.6%) in contrast to 36.2% of NHB and 53.3% of NHW. The utilization of ERs by NHB was the highest among subgroups (51.7%). On the other hand, Hispanic utilization of Medicaid was higher at 67.2 %, followed by NHB with 53.4% in contrast to 20% of NHW. In particular, our findings highlight the healthcare disparities of the NHB group, more so than expected. Healthcare providers, in particular primary care and ER providers, must be educated and enables to be highly suspicious of KS in young children, in particular in API and NHB children, presenting with fever and rash illnesses (Anderson, Todd and Glode 2005).

Only 49.4% of the patients in our sample were correctly diagnosed with KS upon admission to a hospital. Remarkably, the API group was diagnosed in only 22.2% of the cases. With less than 50% of the cases being diagnosed upon admission, we remain deeply concerned with the data revealing 41 different admitting diagnoses other than KS. Given KS' long-term health impact and relative obscurity, a pediatric infectious disease research priority for finding its cause and another for educating providers and the direct community must be developed. Identification of the causative agent(s) would be a promising step toward

developing a diagnostic test and ultimately preventing the disease (Rowley 2006). Meanwhile, KS cases reported annually to the voluntary, "passive surveillance system" at the CDC represented only about 10% of cases diagnosed with KS in the U.S. (Belay et al. 2003). A national "active surveillance system" for KS will facilitate the monitoring of possible nationwide or regional outbreaks and trends in coronary artery abnormalities resulting from KS. Active surveillance may enable better quality of life and potentially increase years of life for KS patients.

This is the first report of Kawasaki Syndrome in Texas since the 1984 Rauch et al. study. Results of this study suggest there is a higher incidence rate based on using hospitalization rate as a proxy than that reported by Rauch et al. for Harris County (Houston, Texas) with 18.8% of all cases and a hospitalization rate of 15.7 per 100,000 children (Lloyd et al. 2001). Rauch et al. reported 61 cases over 3 consecutive years, 1982 to 1984, recording an incidence rate of 9.1 per 100,000 children of less than five years old and using a case control study.

It is compelling that Collin County in DFW has the highest hospitalization rate at 29.1 per 100,000 children who are less than five years of age and at 30.6 per 100,000 children who are less than 1 year old. The racial makeup of Collin County in 2006 included 9.7% of API which might explain this observation (U.S. Census 2008). Our finding that 26.6% of all Texas KS cases are distributed in the cluster of counties composing DFW produces great concern. The current body of evidence does not explain this disproportionate incidence.

Limitations

The number of KS-associated hospitalizations might have been overestimated as multiple KS hospitalizations for single cases were not screened. Inversely, many KS cases

could be missing from database because the disease could have been treated on an outpatient basis, since not all children diagnosed with KS required hospitalization. Many KS patients could have seen by health care providers in urgent care, outpatient, and family care settings and as classical cases or incomplete or atypical KS cases (Newburger et al. 2004). Further, contributing to the possible underestimates of KS cases, THCIC does not collect data from rural hospitals with less than 100 beds.

CONCLUSION

The epidemiological trend of KS in Texas is consistent with national incidence rates. The high incidence of KS in Non-Hispanic Black children (second only to API) is a source of concern, especially since they experience disparities with significant healthcare access problems. No significant difference was found between Hispanic and NHW children in ER use for KS.

In Texas, healthcare providers clearly do not have enough experience or training with KS to adequately identify and treat this disease. The disease appears more frequently in Texas' DFW counties. The disease is not monitored by reporting agencies in Texas. No statewide database is maintained, and an accurate numbers of KS cases are not collected annually by any agency. Support must be established to mandate KS as reportable condition by hospitals. Subsequently, such a mandate will establish a statewide, if not national, database for a disease that clearly has significant public health ramifications. With the misdiagnosis rate more than 50%, educating physicians and other healthcare providers to recognize of the symptoms of KS is imperative, particularly for ER and primary care providers.

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Table 1: Kawasaki Syndrome Associated Hospitalization Rates by Age, Gender and Race/Ethnicity in Texas, 2004

Total	Age group	N=330	%	Hospitalization rate*	Texas Population by age groups
Years of age	<1 year	44	13.3	11.7	375385
	1-4 year	203	61.5	14.3	1417965
	5-9 year	62	18.8	3.8	1620238
	10-14 year	11	3.3	0.6	1730425
	15-17 year	4	1.2	0.4	1028611
	< 5 year	247	74.8	13.8**	914552
	≥5 year	83	25.2	1.8	878798
Gender	males	198	60		
	females	132	40		
Children <1 year by race/ ethnicity					
	Hispanics	23	52.3	12.5	183899
	NHW	7	15.9	8.8	136545
	NHB	6	13.6	14.7**	40847
	API	5	11.4	44.9**	11139
children <5 year by race/ ethnicity					
	Hispanics	107	43.3	12.6	847501
	NHW	66	26.7	9.7	680207
	NHB	37	15	18.4**	201470
	API	16	6.5	29.8**	53731
Age group by gender					
	Male				
	<1	29	65.9	15.1**	191467
	1-4	117	57.6	16.2	723085
Age group by gender					
	Female				
	<1	14	34.1	8.2	183918
	1-4	86	42.4	12.4	694880

* Per 100,000 children * * $p<0.05$. NHW= Non-Hispanic Whites; NHB= Non-Hispanic Blacks; API= Asians and Pacific Islander

Source: Texas Health Care Information Collection (THCIC) and Texas State Data Center for 2004.

Table 2: Risk Mortality, Illness Severity, Admitting Diagnosis, Source of Admission and Payment Source by Race/Ethnicity in Texas, 2004

		Total N (% based on 330)	NHB (% based on 58)	Hispanics (% based on 125)	NHW (% based on 105)	API (% based on 18)
		N %	N %	N %	N %	N %
Risk Mortality	Minor	311 (94.2)	51 (87.9)	120 (96.0)	100 (95.2)	17 (94.4)
	Moderate	13 (3.9)	4 (6.9)	3 (2.4)	4 (3.8)	1 (5.6)
	Major/ Extreme	6 (1.8)	3 (5.2)	2 (1.6)	1 (1.0)	0 (0)
Illness Severity						
	Minor	240 (72.7)	36 (62.1)	90 (72.0)	80 (76.2)	16 (88.9)
	Moderate	72 (21.8)	16 (27.6)	30 (24.0)	19 (18.1)	1(5.6)
	Major/ Extreme	18 (5.5)	6(10.3)	5 (4.0)	6 (5.7)	1 (5.6)
Admitting Diagnosis	Kawasaki Syndrome	163 (49.4)	34 (58.6)	63 (50.4)	54 (51.4)	4 (22.2)
	Fever	107 (32.4)	15 (25.9)	36 (28.8)	33 (31.4)	13 (72.2)
	Rash/Nonspecific Skin Eruption	19 (5.8)	1(1.7)	6 (4.8)	10 (9.5)	1 (5.6)
	Other diagnosis	41 (12.4)	8 (13.8)	20 (16.0)	8 (7.7)	0 (0)
Source of Admission	Physician Referral	161 (48.8)	21 (36.2)	57 (45.6)	56 (53.3)	10 (55.6)
	ER	131 (39.7)	30 (51.7)	52 (41.6)	35 (33.3)	8 (44.4)
	Transfer from Hospital	25 (7.6)	4 (6.9)	10 (8.0)	11 (10.5)	0 (0)
	Other	13 (3.9)	3 (5.2)	6 (4.8)	3 (2.9)	0(0)
Payment Source	Private	155 (47.0)	21 (36.2)	35 (28.0)	76 (72.4)	9 (50)
	Medicaid	149 (45.2)	31 (53.4)	84 (67.2)	21 (20.0)	5 (27.8)
	Self-pay/Indigent	19 (5.8)	4 (6.9)	4 (3.2)	5 (4.8)	4 (22.2)
	Other	7 (2.1)	2 (3.4)	2 (1.6)	3 (2.9)	0 (0)

NHW= Non-Hispanic Whites; NHB= Non-Hispanic Blacks; API= Asians and Pacific Islander

Source: Texas Health Care Information Collection (THCIC) for 2004.
Note: “Private” included any patient who had insurance whether HMO, PPO, CHAMPUS, Blue Cross/Blue Shield, or Commercial Insurance.

Table 3: Texas Counties with More Than 4% of Kawasaki Syndrome Cases in 2004

County	Total Cases	%	Population <18 Years	Hospitalization rate Per 100,000 <18 Years	Population <5 Years	Hospitalization rate Per 100,000 <5 Years	Population <1 Year	Hospitalization rate Per 100,000 <1 Year
Collin	17	5.2	177719	13.1	48176	29.0	9807	30.6
Hidalgo	19	6.1	227814	12.2	72314	18	15977	6.3
Travis	13	4.2	206848	9.4	68233	17.6	14287	42.0
Harris	61	18.8	1028371	8.5	312370	15.7	66148	10.6
Dallas	36	11.5	640376	8.2	199154	16.1	41548	12.0
Bexar	16	4.8	410504	5.5	120029	11.7	24970	0*
Tarrant	16	4.8	444525	5.1	130774	7.7	27172	14.7

* As there was no new born with KS in Bexar in 2004