Mapping the Trends of Kawasaki Disease in Hawai'i from 1996 to 2018

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Abstract

Kawasaki disease is a systemic vasculitis of unknown etiology and is the leading cause of acquired heart disease in children in the developed world. Historically, Hawai'i has had the highest incidence of Kawasaki disease in the United States, likely due to the population's unique ancestral composition. To analyze the epidemiology, demographics and spatiotemporal distribution of Kawasaki disease in Hawai'i, a retrospective chart review was conducted utilizing data from Kapi'olani Medical Center for Women and Children encompassing the period of 1996-2018. A total of 858 patients were analyzed with 877 episodes of Kawasaki disease. On average, 37 episodes of Kawasaki disease were diagnosed annually over the 23-year period. The annual incidence was 32 per 100 000 children <5 years of age. Asian children (66.1%) accounted for the majority of cases, followed by Native Hawaiians and Other Pacific Islanders (16.6%). Unlike Japan and the continental United States, there was no characteristic seasonal pattern in the distribution of Kawasaki disease in Hawai'i, which may be attributed to its tropical climate or the recent changes in global weather patterns. Local geographical differences in the incidence of Kawasaki disease demonstrated that the Windward (Eastern) coast of O'ahu had a higher rate, while the Leeward (Western) coast displayed a lower incidence rate. This could be explained by variations in ethnic composition and weather patterns of certain areas. Future studies could provide geographical weather data and statistical analysis to determine what environmental triggers are correlated with Kawasaki disease trends in the State of Hawai'i.

Keywords

Kawasaki disease, coronary artery dilation, aneurysm, epidemiology, incidence

Abbreviations

CAD = coronary artery dilation
IQR = interquartile range
IVIG = intravenous immunoglobulin
KMCWC = Kapi'olani Medical Center for Women & Children
LAD = left anterior descending coronary artery
RCA = right main coronary artery

Introduction

Kawasaki disease is the most common acquired heart disease of childhood; it primarily affects children below the age of 5 and is characterized by features of systemic vasculitis.[1] The first cases of Kawasaki disease within the United States were recognized in Hawai'i in 1976.[2] The incidence of Kawasaki disease has historically been much higher in Hawai'i than in the continental United States (estimated incidence in United States is 25 per 100 000 children < 5 years of age).[1,3] Higher incidence has been observed in Hawai'i among children of Asian and Pacific Islander ancestry (62.9 per 100 000), with the highest incidence in Japanese children (210.5 per 100 000), similar to that observed in Japan (309 per 100 000 children < 4 years of age).[3-6] However, unlike Japan and the continental United States, where Kawasaki disease has demonstrated seasonal fluctuations with peaks in the winter and spring, no seasonal variation has been observed in Hawai'i to date.[1,3,7,8] Several proposed models have suggested roles for ethnicity, weather patterns, and environmental exposure to 1 or more infectious agents in the global distribution of Kawasaki disease.[8-11] The Hawai'i medical community has played a unique role in the recognition of the illness and in pioneering contributions to the current standard therapy, and still plays an important role in the understanding of ethnic and environmental influences in the development of Kawasaki disease.

This retrospective study provides a comprehensive analysis of the largest cohort to date of children with Kawasaki disease in Hawai'i and one of the largest multi-ethnic cohorts in the country. Patterns in temporal and geographical distribution were investigated to characterize trends in Kawasaki disease since its documentation in Hawai'i and provide insight into future directions for analysis.

Methods

Study Design and Cohort

A retrospective chart review was conducted at the Kapi'olani Medical Center for Women & Children (KMCWC) that included charts from the 23-year period from January 1, 1996 to December 31, 2018. Data were analyzed from every patient admitted with the diagnosis of Kawasaki disease confirmed by an infectious disease specialist. The diagnosis of Kawasaki disease followed the established international diagnostic guidelines for complete and incomplete Kawasaki disease.[1] Complete Kawasaki disease was defined as the presence of fever (T > 38.6 C) for at least 5 days with 4 out of 5 symptoms: rash, cervical lymphadenopathy, conjunctivitis, oral erythema (lips or tongue), erythema of the palms and soles. Incomplete Kawasaki disease was defined as fever with the presence of only 2 or 3 of the above symptoms. In case of incomplete presentation, laboratory studies (such as elevated erythrocyte sedimentation rate) and/or imaging studies (such as coronary artery dilation (CAD) on echocardiogram) were used to confirm the diagnosis of Kawasaki disease. Patients with suspected cases of Kawasaki disease at admission were

excluded from the final analysis if the diagnosis of Kawasaki disease was ruled out prior to discharge. Separate episodes of Kawasaki disease were registered for the same patient (ie, recurrent Kawasaki disease) when the admissions occurred at least 6 months apart. This study was evaluated by the Scientific Review Committee of Hawai'i Pacific Health and was found to be exempt from requiring informed consent.

Data Collection

Patient demographics (age, and self-reported gender, ancestry, and zip code), clinical characteristics (height, weight, date of admission, date of fever onset), laboratory findings (white blood cell count, C-reactive protein level, erythrocyte sedimentation rate, albumin level), IVIG resistance, complete vs. incomplete presentation of Kawasaki disease and echocardiogram values (date of echocardiogram, internal dimensions of the left anterior descending coronary artery (LAD) and right main coronary artery (RCA)) were collected from every study subject at the time of diagnosis. IVIG resistance was defined as the persistence or recrudescence of fever ≥ 36 hours after the completion of IVIG treatment. Complete or incomplete presentation of Kawasaki disease was defined following the American Heart Association guidelines.[1] Ancestry was self-reported by the family and only the single most prominent ancestral or ethnic background was included in the results and table. The self-reported ancestry was extracted from the admission notes and not from the automated electronic database, therefore it reflects more accurately the most prominent ancestry of the patients. Z-scores were calculated for coronary artery dimensions (LAD and RCA) using the Boston formula.[12] Coronary artery dilation was determined by a coronary artery (RCA or LAD) internal diameter z-score of ≥2.0 or, for patients admitted prior to 2006, by the explicit statement of the presence of CAD in the echocardiogram report.

Seasonal and Geographical Analysis

Episodes of Kawasaki disease were analyzed by temporal distribution. Fever onset was used to indicate the onset of illness for patients admitted from 2007 to 2018. Due to the inconsistency in which the date of fever onset was reported in medical records during the first decade of the study period, the date of admission was instead utilized to indicate the onset of illness for patients admitted from 1996 to 2006. Temporal distribution of Kawasaki disease episodes was assessed by seasons with annual cut-offs determined by the dates of the solstice and equinox: spring (late March to mid-June), summer (late June to mid-September), autumn (late September to mid-December) and winter (late December to mid-March), by calendar years, "decades" (1996-2006 and 2007-2018) and for the overall study period. Geographical analysis was performed using self-reported zip codes at the time of admission for Kawasaki disease. Subjects were excluded from the seasonal or geographical analyses if the fever onset occurred in a foreign country or within the continental United States.

Statistical Analysis

Categorical variables were expressed as frequency and percentage, and continuous variables were expressed as median, interquartile range, and range. Annual occurrence of Kawasaki disease (admissions) was depicted with a linear graph. Seasonal variation of Kawasaki disease occurrence was analyzed and depicted as a box plot with median and interquartile ranges. Geographical distribution was expressed as the sum of all cases originating from the self-reported zip codes. Excel version 16 (Microsoft Corp: Redmond, WA) was used for statistical calculations.

Results

Cohort Characteristics

This study collected data from every patient admitted with Kawasaki disease to the single tertiary pediatric hospital in the State of Hawai'i between 1996 and 2018. There were 927 patient charts reviewed, and the final cohort consisted of 858 patients with a total of 877 episodes or occurrences of Kawasaki disease, accounting for 19 (2.2%) recurrent episodes (Table 1). There were 479 (55%) males and 398 (45%) females among the 877 admissions, resulting in a male to female ratio of 1.2:1. Most episodes occurred in subjects less than 5 years of age (n = 728, 83%) and 217 (25%) episodes occurred in infants less than 1 year of age. The most common self-reported ancestry was Asian (n=580, 66%), with Japanese (n = 253, 29%) and Filipino (n = 162, 19%) ancestries being the most prevalent. Native Hawaiian or Other Pacific Islander ancestry was self-reported in 146 (17%) episodes. Seventy-two percent of patients reported more than one ancestry or ethnicity (ie, multi-ethnic), in which cases only the most prominent ancestral or ethnic background was included in the analysis. Incomplete presentation of Kawasaki disease was registered in 243 (28%) episodes. IVIG resistance occurred in 125 (14.3%) episodes.

Coronary Artery Dilation

Of the final cohort (n = 877), 187 (21%) episodes had a presence of CAD during the initial evaluation, at the time of admission or diagnosis of Kawasaki disease (Table 1). Episodes from 2006-2018 (n = 477) were further stratified by z-scores. Of these 477 episodes, abnormal coronary arteries with a z-score exceeding 2.0 were present in 126 (26%) episodes. CAD (z-score ≥ 2.0 and < 2.5) occurred in 34 episodes (7%), and small (z-score ≥ 2.5 and < 5.0), medium-sized (z-score ≥ 5.0 and < 10.0) and giant aneurysms (z-score ≥ 10.0) occurred in 77 (16%), 13 (3%), and 2 (0.4%) of the episodes at the time of diagnosis, respectively.

Laboratory Markers

Inflammatory markers were elevated at the time of Kawasaki disease diagnosis with the median C-reactive protein level of

Table 1. Study Cohort Characteristics (1996-2018)		
		N or median (% or IQR)
Episodes		877
Recurrent episodes		19 (2.2%)
Time between recurrent episodes (years)		2.5 (1.4-4.1)
Female		398 (45.4%)
Age (years)		2.1 (1.0-4.1)
Age distribution	< 6 months	79 (9.0%)
	≥ 6 months & < 12 months	138 (15.7%)
	≥12 months & < 5 years	511 (58.3%)
	≥ 5 years	139 (15.8%)
	Unknown[a]	10 (1.1%)
Ethnicity	Asian	
	Japanese	253 (28.8%)
	Filipino	162 (18.5%)
	Chinese	65 (7.4%)
	Korean	23 (2.6%)
	Vietnamese	15 (1.7%)
	Other Asian	62 (7.1%)
	Native Hawaiian or Pacific Islander	146 (16.6%)
	White or Caucasian	84 (9.6%)
	Black or African American	8 (0.9%)
	Hispanic or Latino	11 (1.3%)
	Unknown	48 (5.5%)
	Multiethnic[b]	633 (72.2%)
Time of fever onset to date of admission (days)		4 (3-6)
Kawasaki disease diagnosis	Complete	555 (63.3%)
	Incomplete	243 (27.7%)
	Unknown	79 (9.0%)
Coronary artery dilation (entire cohort, Z-score ≥2.0)[c]	187 (21.3%)	
Coronary artery Z-scores (patients from 2006-2018 only, N=477)****	Total ≥2.0	126 (26.4%)
	≥2.0 and <2.5	34 (7.1%)
	≥2.5 and <5.0	77 (16.1%)
	≥5.0 and <10.0	13 (2.7%)
	≥10.0	2 (0.4%)
White blood cell count (cells/μL) (normal 4,000-11,000 /uL)		13 8000 (10 700-17 000)
C-reactive protein (mg/L) (normal < 3 mg/L)		29.3 (8.5-88.6)
Erythrocyte sedimentation rate (mm/hour) (normal < 10 mm/hour)		70 (50-91)
Albumin (g/dL) (normal 3.6-5.4 g/dL)		3.8 (3.4-4.1)
Low albumin (<3.6 g/dL)		244 (27.8%)
IVIG Resistance		125 (14.3%)

[a] Age was unknown for 10 episodes due to data limitations.
[b] The majority of patients (72%) reported more than 1 ancestry/ethnicity, however every patient and every episode was counted only once with the most prominent self-reported ancestry/ethnicity.
[c] Before 2004, coronary artery dilation (CAD) was assessed using the Japanese Ministry Criteria, which categorized an internal dimension of < 4 mm as normal, or by subjective assessment. Because this study spans from 1996-2018, the prevalence of CAD (21.3%) may underestimate the actual incidence of CAD. There were 14 additional patients that had no Z-score data or lacked sufficient information to calculate a Z-score.

29.3 mg/L (normal < 3 mg/L) and the median erythrocyte sedimentation rate of 70 mm/hour (normal < 10 mm/hour) (Table 1). Low albumin, defined as <3.6 g/dL, occurred in 244 (27.8%) episodes (median 3.8 g/dL, IQR 3.4-4.1 g/dL).

Seasonal Distribution

The occurrence of Kawasaki disease in Hawai'i (number of admissions to KMCWC) varied from year to year over the last 2 decades with the median number of annual episodes of 37 (IQR 32-43) (Figure 1). There was a spike in 2010 with 62 episodes, accounting for a 51% rise from 2009, followed by a 42% decline in 2011. In the remainder of the 23-year period, the number of episodes ranged from 25 to 46 episodes annually. The incidence of Kawasaki disease in children less than 5 years of age was 32.3 in 2017 and 30.8 in 2018.

There was no significant seasonal difference (spring vs summer vs. autumn vs. winter) in the occurrence of Kawasaki disease over the entire study period. However, a separate analysis of the number of episodes during the first 11 years of the study period revealed a significantly higher number of episodes in the winter months (n=13, IQR 10-16) compared to the summer months (n=8, IQR 6.5-9.5) (Figure 2). From 2007-2018, peak activity was observed in the summer (n=10.5, IQR 9-12) and fall months (n=10, IQR 8.5-11.5) compared to the winter months (n=8, IQR 5.5-11.5) without statistical significant difference.

Geographical Characteristics

Of the final cohort of 877 episodes, 851 (97%) had zip codes reported within the State of Hawai'i. Of these 851 episodes, 704 (82.7%) occurred on O'ahu, 74 (8.7%) on the Big Island, 36 (4.2%) on Kaua'i, 33 (3.9%) on Maui and 4 (0.5%) on Moloka'i (Figure 3). For the island of O'ahu, the zip codes with the highest number of episodes were 96789 (n=65), 96744 (n=62), and 96797 (n=62). These zip codes are located in Central O'ahu and the Windward (Eastern) coast of the island. The lowest number of episodes were observed on the North Shore and Leeward (Western) coast.

The total number of episodes in every zip code was adjusted for the total population of the selected area based on the census data from 2018. The highest incidence of Kawasaki disease adjusted for the population of the area was on O'ahu (72.3/100000 inhabitants). Within O'ahu, the highest incidence of Kawasaki disease episodes was observed in the central and Windward regions.

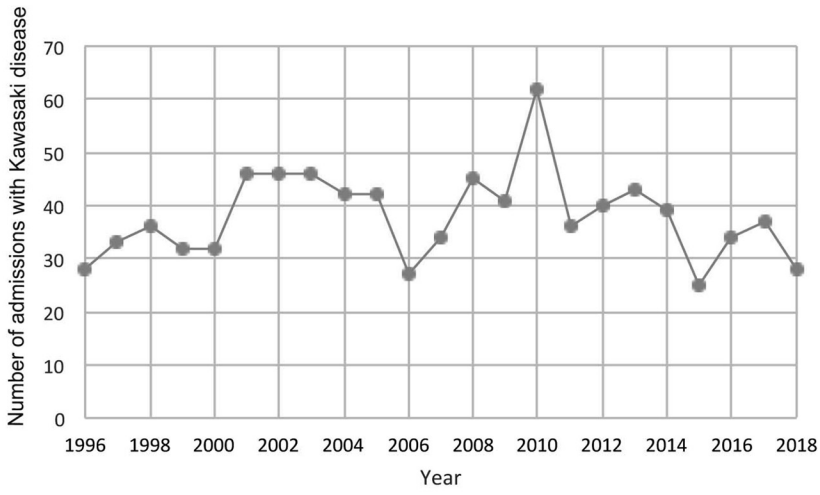

Figure 1. Annual Changes in the Number of Admissions with Kawasaki Disease from 1996 to 2018.

Analysis of the 23-year period revealed that the average occurrence of Kawasaki disease was 37 episodes / year with notable year-to-year variation (range: 25-62 episodes).

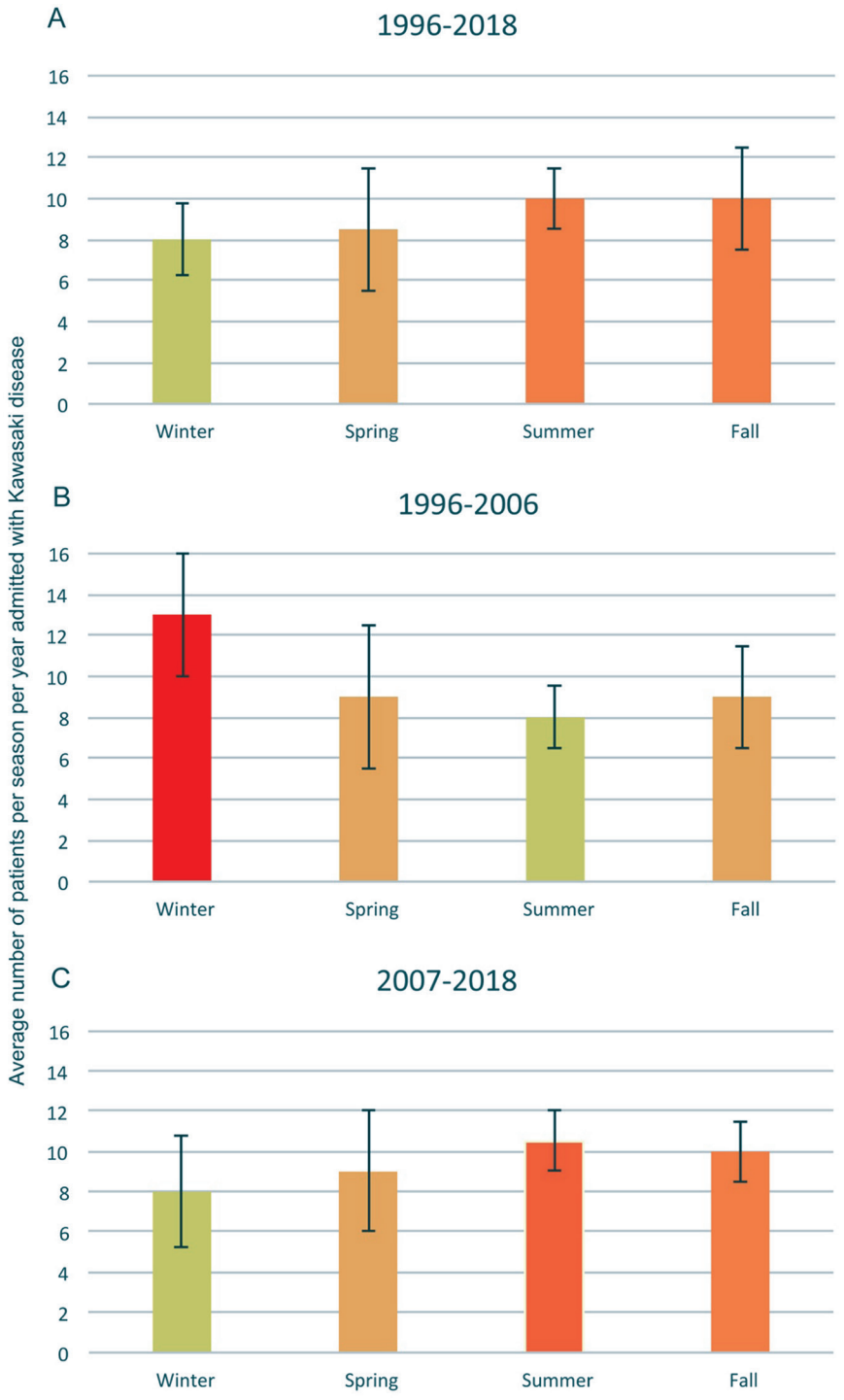

Figure 2. Seasonal Changes in Kawasaki Disease from 1996 to 2018.

A: The average annual number of episodes in the 4 seasons showed no recognizable pattern in the seasonality of Kawasaki disease for the period of 23 years.

B: The separate analysis of the 1996-2006 period revealed a characteristic peak of Kawasaki disease episodes in the winter, significantly higher than in the summer.

C: The analysis of 2007-2018 did not show the same trend: Kawasaki disease occurred slightly more often in the summer and autumn, as compared to the winter (not statistically significant).

The boxes indicate the median and the bars indicate interquartile range.

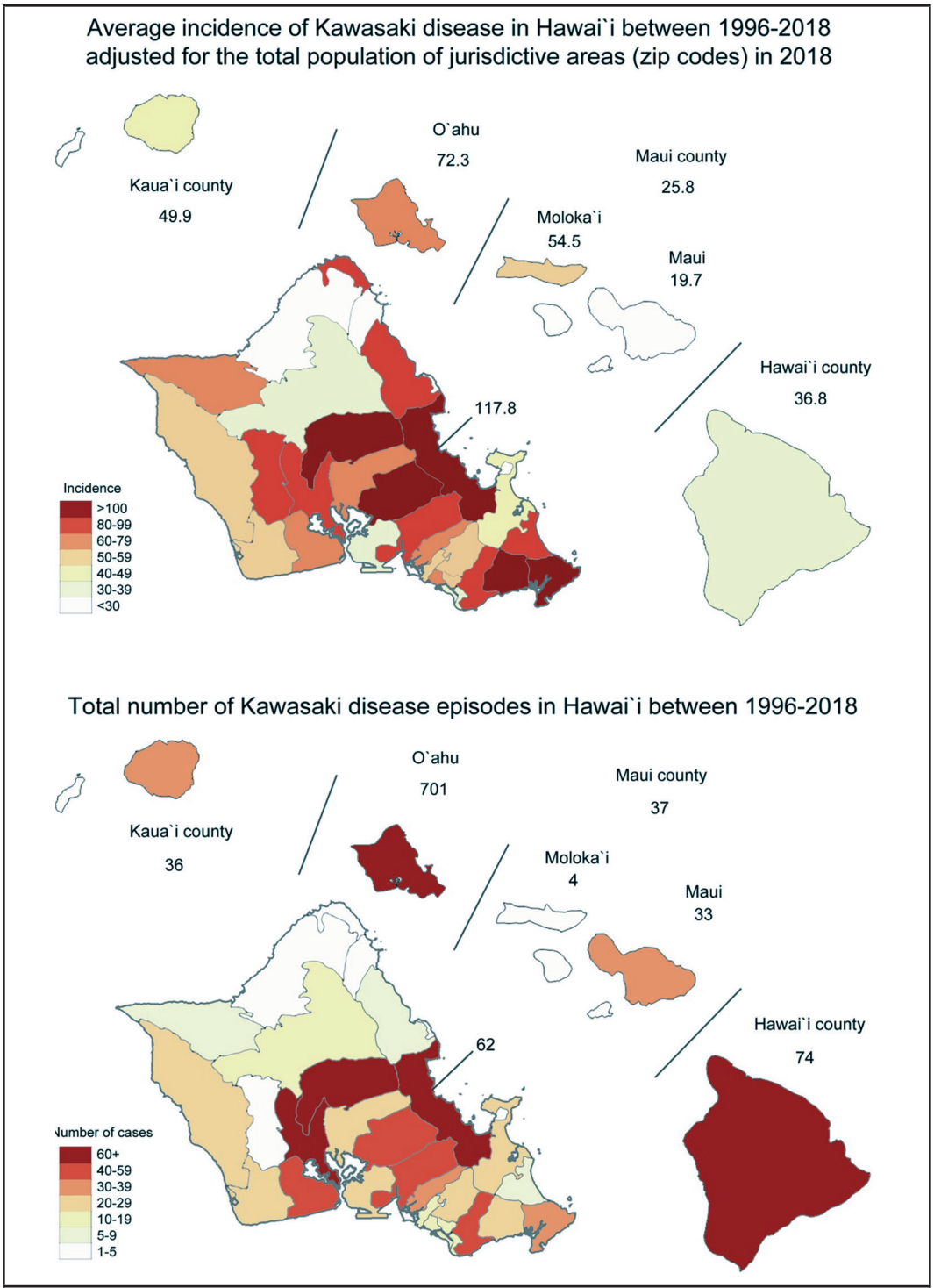

Figure 3. Geographical Distribution of Kawasaki Disease within Hawai'i from 1996 to 2018.

Top: The average annual rate of Kawasaki disease corrected by the population size in 2018 showed that the highest incidence was again in the Windward (Eastern) and Central areas of O'ahu.

Bottom: The highest number of Kawasaki disease episodes occurred on O'ahu, followed by Hawai'i and Kaua'i. Within the island of O'ahu, most cases were registered from the Windward (Eastern) and central regions of the island.

Discussion

A comprehensive evaluation of admissions with Kawasaki disease to the single tertiary pediatric hospital in Hawai‘i in the last 23 years revealed an average annual occurrence of Kawasaki disease of 37 with an estimated annual incidence of 32 in 100 000 children less than 5 years of age.

The incidence of Kawasaki disease continues to be significantly higher in Hawai‘i compared to the continental United States (estimated incidence in the United States is 25 per 100 000 children < 5 years of age).[1,3,13] Our study estimated the incidence at 31-32 in 100 000 children < 5 years of age in the last 2 years of analysis. This is very close to what previous studies have found including the analysis of hospital discharge records with Kawasaki syndrome from 25 acute-care hospitals in Hawai‘i.[3]

The cohort characteristics described in this study are also consistent with previous literature. In this study, 83% of admissions were children < 5 years of age and 25% were < 1 year of age, similar to the data reported by local and national studies.[1,11,13] Kawasaki disease has been widely reported to occur in males more frequently than females. This study found a male to female ratio of 1.2:1, comparable to previously reported ratios of about 1.3-1.7:1.[1,3,6,11] The most prevalent self-reported ancestries were Japanese (29%), Filipino (19%), and Native Hawaiian or Pacific Islander (17%), which is consistent with previous reports.[1,3,6,11] The ethnic composition of patients with Kawasaki disease is somewhat different that the overall composition of the population of Hawai‘i (38.6% Asian, 24.7% Caucasian, 10% Native Hawaiian or Pacific Islander), likely due to the higher prevalence of Kawasaki disease in patients with East Asian ancestry. The recurrence rate (2.2%) reported in this study falls between the rates previously reported in North America (1%) and Japan (3%).[3] The IVIG resistance rate (14%) observed in this study is comparable to rates in previous reports of 10%-20%.[1,6] The overall rate of CAD was 21% for the entire study period, similar to the American Heart Association’s Scientific Statement in 2017 of 23%.[1] The rate of CAD during 2006-2018 was 26%, which is significantly higher than the 16% during the first decade. This can be explained by differences in the assessment of the coronary arteries: Before 2004, CAD was assessed by the Japanese Ministry of Health Criteria, which categorized an internal dimension of < 4 mm as normal, or by subjective assessment. After 2004, coronary arteries were assessed using standards and z-scores.

Seasonal Characteristics

A characteristic winter peak of Kawasaki disease episodes was observed between 1996 and 2006 in Hawai‘i, but this seasonal pattern was not present between 2007 and 2018. Holman and colleagues examined the incidence of Kawasaki disease among children in Hawai‘i from 1996 to 2006 based on data from the Hawai‘i State Department of Health. Consistent with our findings, they acknowledged the presence of a small peak in the hospital admissions for children < 5 years of age seen in December and January. This trend did not continue into 2007-2018 based on our analysis, and the reason could be a shift in the climate.

Burns and colleagues investigated the seasonality of Kawasaki disease through a comprehensive analysis from 25 countries across the globe, including data gathered from Hawai‘i between the years of 1996-2011. Although time series from countries within the Northern Hemisphere contained statistically significant seasonal variations in Kawasaki disease activity with peaks from January to March, the tropics and Southern hemisphere did not show the same seasonal pattern.[8] In particular, Hawai‘i’s location falls within the tropics and was determined to be “non-seasonal” by the autoregressive/moving average (ARMA) time series model.[8] Consistently, the overall assessment of the last 23 years of Kawasaki disease onset in Hawai‘i showed no recognizable seasonal pattern.

Kawasaki disease has been hypothesized to be triggered by one or more infectious agents. Multiple studies have suggested the role of tropospheric wind patterns in the transport of potential agents.[8-10] Exposure to fungal toxins or other environmental factors from Northeastern China may be related to the epidemiological patterns observed in Japan, Hawai‘i, and San Diego.[10] Further studies in Hawai‘i could focus on the occurrence of Kawasaki disease within the last decade in relation to changing local and global weather patterns.

Geographical Characteristics

The majority of residents in the State of Hawai‘i live on O‘ahu, so as expected, most cases of Kawasaki disease were found on O‘ahu. However, even after adjusting for the population of jurisdictive areas (zip codes), the highest rate of Kawasaki disease relative to the total residents of an area was found on O‘ahu. Health care accessibility is greatest on O‘ahu, which could suggest that there are simply more recorded cases in areas with more developed health care systems. Manlhiot and colleagues concluded that patients with Kawasaki disease were more likely to live in urban areas, and in environments with low exposure to environmental antigens such as fungi and spores.[9] O‘ahu is the island with the most industrial development, and the high number of cases could be concurrent with this finding. Using this theory, we would conversely expect to see fewer cases in more rural islands, consistent with our findings of having the fewest cases of Kawasaki disease per residents in Moloka‘i, Kaua‘i and areas of Maui and the Big Island.

Weather patterns could provide further explanations for the geographical variation of Kawasaki disease in Hawai‘i. Large scale wind currents are linked to the illness, suggesting that the trigger could be wind-borne.[10] The windward (Eastern) coast of O‘ahu represents a large portion of the total number of cases, and

its climate is generally windy and rainy with cool temperatures. The Leeward (Western) coast of O'ahu had significantly fewer cases, and its climate is dry and hot with little vegetation. Future studies could provide detailed geographical data to determine if wind, temperature, or precipitation is related to the occurrence of Kawasaki disease in Hawai'i.

Study Limitations

This study may underestimate the incidence and registered episodes of Kawasaki disease because patient records were obtained and analyzed only from the single tertiary pediatric hospital in the state and did not include admissions to other hospitals, nor children who could have been diagnosed with Kawasaki disease but were not admitted to any hospital with the illness. Ancestry and residence were self-reported resulting in possible inaccuracy of the collected information.

Data collection and analysis from the first decade were limited for the following reasons: Some of the handwritten medical records kept on microfilm or compact disc were incomplete, and therefore the analysis of laboratory markers and echocardiogram findings were limited in a small percentage of study subjects. Coronary artery dilation before 2006 was assessed subjectively following the Japanese Ministry of Health criteria and therefore may have underestimated the rate of CAD. Due to the lack of consistent reporting in the date of fever onset from the first decade, the date of admission was utilized as an indication for the onset of illness, which may have resulted in a minimally altered seasonal distribution pattern.

Conclusions

Hawai'i has the highest incidence of Kawasaki disease in the United States, likely due to the unique ancestral composition of its population. There is no characteristic seasonal pattern in the distribution of Kawasaki disease in Hawai'i, which may be attributed to its tropical climate or the recent changes in global weather patterns. Local geographical differences in the incidence of Kawasaki disease in Hawai'i could be explained by the particular ethnic composition of certain areas and/or local weather characteristics.

Conflict of Interest

None of the authors have any conflict of interest.

Acknowledgments

The authors would like to acknowledge Mrs. Andrea Siu, Dr. Chieko Kimata and Mr. Ka Hon Lau for their help in extracting the data from the medical records.

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