NEWBORN MICROCEPHALY: HOW OFTEN IS IT DIAGNOSED IN LAC?
A FIVE-YEAR REVIEW OF COUNTY HOSPITALIZATIONS WITH A MICROCEPHALY DIAGNOSIS

ABSTRACT

Background

Zika infection has been identified among California's pregnant travelers, which may lead to an increased rate of microcephaly in the state and in Los Angeles County (LAC). Currently, there are no published rates of newborn microcephaly for LAC, description of the racial-ethnic populations affected, nor reports of severity of disease. The national microcephaly rate is estimated to range from 2-12 babies per 10,000 live births. We performed an analysis of microcephaly hospitalizations to establish a baseline, trend, and severity of LAC patients diagnosed with microcephaly.

Methods

A total of five years of microcephaly hospitalizations were reviewed using a hospital discharge dataset obtained from the California Office of Statewide Health Planning and Development (OSHPD). A newborn microcephaly case was defined as any newborn seen at an LAC hospital from 2010-2014 and had a discharge diagnosis of microcephaly. Annual rates of newborn microcephaly were calculated using LAC birth data, and rates were stratified by race-ethnicity. Burden indicator variables such as length of stay, hospital charge, and fatality rate were compared by gender and race-ethnicity.

Results

We identified 274 newborns hospitalized in LAC with microcephaly over the five-year study period (mean: 54.8 per year, range: 42-67 per year). The newborn microcephaly rate for LAC was 4.2 per 10,000 live births. Rates were higher among African American newborns (9.0 per 10,000 live births), female newborns (5.4 per 10,000 live births), and highest among female African American newborns (11.8 per 10,000 live births). The case fatality rate among all microcephaly newborns was 5.8% (16/274) and was higher among female infants (6.5%, 11/170).

Conclusions

This review identified a newborn microcephaly rate in LAC similar to the national rate for babies. These findings indicate that microcephaly in LAC can be severe and disproportionately affects African American and female newborns. More study is needed to corroborate these findings and to better understand the causes of these racial disparities among microcephaly newborns in LAC.

INTRODUCTION

Microcephaly is a condition where an infant's head circumference is at least two standard deviations less than an infant of the same gender and age [**1**]. This condition may be accompanied by other major birth defects such as hearing and visual loss but can occur with no other health conditions. Microcephaly can occur because a baby's brain has not developed properly during pregnancy or has stopped growing after birth. The cause of microcephaly is unknown in most cases. Conditions associated with microcephaly include infections during pregnancy (rubella, toxoplasmosis, cytomegalovirus, Zika virus), severe malnutrition, exposure to toxins (alcohol or other drugs), certain genetic defects (autosomal, recessive, primary microcephaly), or interruption of the blood supply to the baby's brain during development.

Zika infection during pregnancy is associated with increased rates of microcephaly in the resulting newborn [**2, 3, 4, 5, 6**]. Zika infection has been identified in over 45 pregnant California residents who have traveled to endemic areas [**7**]. Due to the mild and often asymptomatic nature of this infection, many pregnant women who are infected are likely undiagnosed. The impact of this disease on newborns in California and LAC remains unclear.

Currently, there are no published rates of newborn, neonate, or infant microcephaly in LAC or California. The Centers for Disease Control and Prevention (CDC) estimates that there are between 2-12 cases of microcephaly per 10,000 per live births nationally [**1**]. Using this national microcephaly estimate with the approximately 124,000 live births in LAC [**8**], we can estimate that the crude rate of microcephaly in LAC babies is 25-149 cases annually. However, this estimate does not take into consideration the risk factors among LAC residents that may be different from those found nationally. It also does not distinguish newborn rates from infants diagnosed after delivery.

A better estimate for the number and rates of newborns, neonates, and infants diagnosed with microcephaly in LAC needs to be established. This will help with monitoring changes in these numbers and lead to a better understanding of the impact of Zika on infants. Data on all hospitalizations in LAC is available through the OSHPD and should be useful in establishing microcephaly rate estimates.

METHODS

A dataset of all hospitalizations occurring in LAC hospitals with a diagnosis of microcephaly was created. This microcephaly dataset was created from a dataset of all LAC hospitalizations obtained from the OSHPD. Although the dataset is de-identified, it contains information on each patient's age, race, length of stay, outcome (survived vs. died), hospitalization charge, and diagnoses (up to 24 diagnoses). Since birth only happens once, patients coded as being born in the hospital they were discharged from can be considered individual patients, and rates may be calculated.

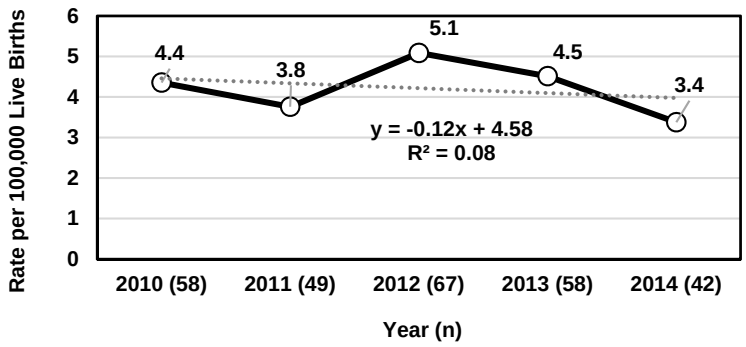
We defined a case of newborn microcephaly as any patient seen at an LAC hospital from 2010-2014, had a discharge diagnosis of microcephaly (ICD9 code = 742.1), and was born in the hospital from which they were discharged. A source admission code of 712 (7=newborn, 1=this hospital, 2=not ER) for 2011-2015 data, and the source admission code of 7 (newborn in admitting hospital) for 2010 data was used to select for newborns. Annual rates of newborn and infant microcephaly were calculated using LAC birth data and rates. Denominator data on annual births and demographic characteristics of newborns in LAC was obtained [**7**]. Rates of newborn microcephaly were compared by gender and race-ethnicity. Indicators for

disease severity (length of hospitalization, hospitalization charge, and case fatality rate) were compared by race-ethnicity and gender. We also reviewed the annual trend of hospital discharges with a diagnosis of microcephaly for patients of all ages.

Results - *Newborn* Microcephaly Cases (n=274)

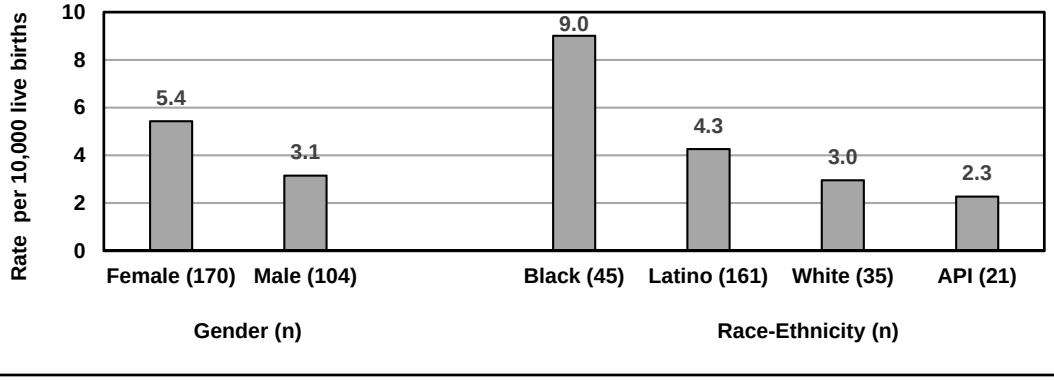
There were 274 newborns diagnosed with microcephaly over the five-year study period, representing unique infants diagnosed for the first time. The number of newborn cases ranged from 42-67 per year (mean 54.8) and was relatively stable over the study period (data not shown). The annual newborn microcephaly rate was also stable over time, ranging from 3.4-5.1 per 10,000 live births per year and an average rate of 4.2 per year per 10,000 live births (274 infants/648,014 live births) (Figure 1).

Figure 1. Newborn Microcephaly Rate by Year LAC, 2010-2014



The microcephaly rate was higher among female compared to male newborns (5.4 vs. 3.1 per 10,000 live births, rate ratio 1.7) (Figure 2). By race-ethnicity, the highest microcephaly rate was identified among African American infants (9.0 per 10,000 live births), which was greater than twice that of Latino newborns, the race-ethnicity group with the second highest rate (4.3 per 10,000 live births). The rate was higher for African American female (n=29) compared to African American male (n=16) newborns (11.8 vs. 6.3 per 10,000 live births). The rates for other female race-ethnicity categories were closer to the overall rate.

Figure 2. Rates of Newborn Microcephaly by Gender and Race-Ethnicity LAC, 2010-2014



***API refers to Asian Pacific Islanders**

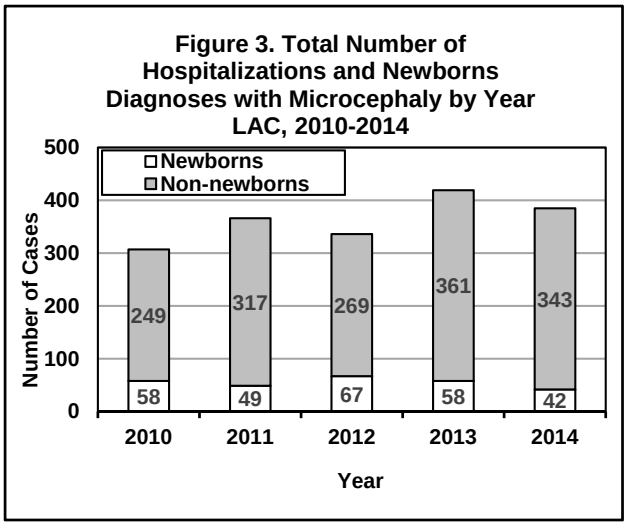
The median length of hospital stay for a newborn with microcephaly was 4 days (mean 12.1 days). The median length of stay was longer for African American newborns (8 days) as compared to White (4 days), Latino (4 days), and Asian newborns (4 days). There appeared to be no difference in length of stay by gender (both with a median of 4 days). The median hospitalization charge for a newborn with

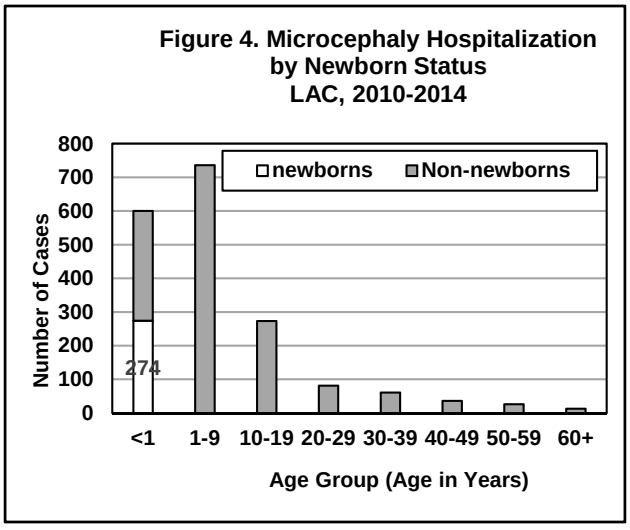
microcephaly was $26,346 (mean $125,068). The median charge was higher for African American newborns ($47,145) than Latino ($24,337), White ($20,280) and Asian newborns ($15,569). The median charge was comparable by newborn gender ($25,092 male vs. $25,339 female). The case fatality rate for a newborn with microcephaly was 5.8% (16/274). The fatality rate was higher for female (6.5%, 11/170) than male newborns (2.9%, 3/104). The rate was also higher for African American (7.6%, 3/29) and Latino newborns (7.4%, 12/161). The number of deaths among White and Asian Pacific Islander (API) newborns were too small to calculate stable rates (≤1).

RESULTS - <u>All</u> Patients Hospitalizations Diagnosed with Microcephaly (n=1813)

We identified 1,813 microcephaly-associated hospitalizations in LAC from 2010-2014. The annual number of microcephaly-associated hospitalizations ranged from 307-419 per year (mean 362.6 per year), increasing slightly over time (Figure 3). Patients ranged in age from newborn to 88 years old (mean age 7.6 years, median age 3 years), and most were older than one-year-old (67%) (Figure 4). There were 598 hospitalizations for infants under one-year-old (33%), including 361 for neonates under one month old (20%) and 274 newborns (15%). The total number of hospitalization days exceeded 17,000 days (annually 3,515 days, mean number of days per patient 9.7 days, median 4 days). A total of fifty deaths were identified: 30 infants, 16 newborns, 4 non-infants. Latino infant deaths accounted for 68% of the total deaths for patients diagnosed with microcephaly (34/50).

With the exception of newborn hospitalizations, which represent unique infants diagnosed for the first time, all other hospitalizations may be due to initial diagnosis or subsequent diagnosis for the same patient. De-duplication is needed to be able to calculate the unique number of microcephaly neonates (≤1 month of age) and infants (≤1 year of age), which is not possible due to the de-identified nature of this dataset. However, an upper limit for the rate of infants diagnosed with microcephaly can be calculated assuming all infant hospitalizations are for a unique patient: 9.2 microcephaly cases per 10,000 live births (598 infants/648,014 live births).





DISCUSSION

In this study, we identified an LAC baseline rate of newborn microcephaly of 4.2 per 10,000 live births (55 cases annually). This rate is similar to the nationally estimated microcephaly rate of 2-12 babies per 10,000 live births reported by the CDC. Because no definition of "babies" is provided with this estimate, the rate identified in our study for newborns may not be directly comparable. A clearer national microcephaly rate is needed for newborns, neonates, and infants diagnosed with microcephaly. The results of this study indicates that many patients may be diagnosed later in life.

This study identified a higher rate of newborn microcephaly among African Americans (9.0 per 10,000 live births) than newborns of other race-ethnicity groups. African American newborns with microcephaly also had a longer, costlier hospital stay with a higher fatality rate than newborns of other race-ethnic groups, indicating that this group is more severely impacted by the disease. More study is need to understand the causes for this trend in this race-ethnicity group. The higher rates of microcephaly identified among African American newborns is a trend consistent with other findings of low birth weight and higher infant mortality rate in this race-ethnicity group [**8**].

This study also identified a higher rate of newborn microcephaly and higher case fatality rate among female newborns (5.4 per 10,000 live births). This finding is consistent with another recent study of 32 microcephalic infants associated with Zika infection in Brazil [**4**] where 69% of the cases were female (n=22). More study is needed to confirm this gender trend. One possible explanation for this trend includes a sex-linked gene responsible for at least some microcephaly cases. A less likely, but plausible, explanation would be a prenatal infection such as Zika, toxoplasmosis, or cytomegalic virus infection affecting the developing fetus and having a differential fetal impact by gender. However, other indicators of disease severity such as length of hospital stay and hospital charges were not higher among female newborns.

CONCLUSION

We were able to establish the annual number and rate of newborn microcephaly in LAC using the OSHPD dataset. Our study identified African American newborns as having a higher rate of microcephaly and more severe illness than newborns of other race-ethnicity groups. However, more research is needed to corroborate these findings. Additional research is needed to establish a microcephaly rate for neonates and newborns in LAC that could not be done with this de-identified dataset.

LIMITATIONS

The definition of microcephaly may vary by clinician and by region [**1, 9**] and may affect the results presented here. In addition, the race-ethnicity of newborns is reported by the parent(s). If the parent is unwilling or unable to declare the infant's race-ethnicity, then the mother's race is reported. This may bias the microcephaly rates by race shown here.

ACKNOWLEDGEMENTS

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REFERENCES

1. Facts about Microcephaly CDC website: http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html

2. Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. de Araújo, Thalia Velho Barreto et al. The Lancet Infectious Diseases. June 15, 2016. Volume 0, Issue 0.

3. Available Evidence of Association between Zika Virus and Microcephaly. Wu J, Huang DY, Ma JT, Ma YH4, Hu YF. Chin Med J (Engl). October 2016;129(19):2347-56. doi: 10.4103/0366-6999.190672.

4. Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy — Brazil, 2015 MMWR Weekly / March 11, 2016 / 65(9);242–247.

5. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. May 2016. Cauchemez, Simon et al. The Lancet, Volume 387, Issue 10033, 2125 – 2132.

6. CDPH Weekly Update on Number of Zika Virus Infections in California. September 2, 2016. http://www.cdph.ca.gov/HealthInfo/discond/Documents/TravelAssociatedCasesofZikaVirusinCA.pdf

7. Maternal birth data obtained from: 2014 California DPH Birth Statistical Master File for Los Angeles County Residents.

8. Los Angeles County Partnership to Eliminate Disparities in Infant Mortality Action Learning Collaborative, Los Angeles County Maternal, Child, & Adolescent Health Program http://publichealth.lacounty.gov/mch/reproductivehealth/PEDIM%20ALC%20Website.pdf

9. Prenatal screening for microcephaly: an update after three decades. Gelber SE, Grünebaum A, Chervenak FA.J Perinat Med. 2016 Sep 23. doi: 10.1515/jpm-2016-0220.