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CORRESPONDENCE

Seasonality of birth month in patients diagnosed with Langerhans cell histiocytosis (LCH)

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Langerhans cell histiocytosis (LCH) is a rare disease with a wide range of clinical manifestations and prognoses. LCH is classified by organ involvement, with single-system and low-risk multisystem disease survival being near 100% and multi-system high-risk disease much lower at approximately 85%[1]. LCH has recently been identified as an inflammatory myeloid neoplasia, though research continues into how immune dysregulation contributes to disease severity.

LCH has a wide range of symptoms and clinical presentations, though lesions are histiologically indistinguishable regardless of disease severity. Activating somatic mutations in the MAPK pathway, in particular BRAFV600E, are found in a majority of LCH cases[2,3]. It has also been hypothesized that high-risk LCH arises from somatic mutation of a hematopoietic progenitor, whereas low-risk disease arises from somatic mutation of tissue-restricted precursor dendritic cells[4]. However, some argue that LCH may also have a reactive component. For example, a high percentage of IL-17A-positive monocytes in peripheral blood found in LCH patients suggests IL-17A may be involved in some pathogenic mechanisms; these monocytes also showed increased mRNA levels for IL-17A[5].

In order to better understand the inflammatory component of LCH, we examined birth month in patients with LCH aiming to hypothesize potential environmental factors that could promote onset of LCH. For example, vitamin D is known to have pleotropic effects and vitamin D deficiency is a contributing factor in autoimmunity and immune modulation[6–9]. Moreover, vitamin D metabolism and function have been found to be dysregulated in many types of cancer[10]. Furthermore, studies have shown that birth month frequently correlates with vitamin D levels, which vary not only according to geographic region, with those residing in the most northern/southern location exhibiting the lowest levels, but also by season. Therefore, birth month could also be a contributing factor in occurrence of inflammatory and autoimmune disease. In particular, data have shown that patients born during late spring or early summer appear to be at an increased risk of developing diseases such as Multiple Sclerosis (MS)[11]. Through our own investigation of the seasonal dependence of birth month, we found a trend showing a greater proportion of late spring and early summer births associated with LCH patients compared to controls. This trend was correlated with the age of onset of LCH.

A database of 147 cases of histiocytosis, including LCH, was compiled from patients or their parents who are members of histiocytosis support groups on Facebook. Of the 121 LCH cases, two did not report the patient's age and another their birth month, yielding a study population of 118 (Table 1). The age of disease onset ranged from newborn to 67 years with a median of 3 years. The geographic distribution is predominantly in the USA ($n = 94$), with the remainder in Europe ($n = 10$), Australia ($n = 5$), Canada ($n = 3$), Asia ($n = 3$), the Middle East ($n = 1$), and unspecified Northern hemisphere ($n = 2$). Assuming that any seasonal variation has a latitudinal dependence, we shifted the birth month of the Australian patients by 6 months.

Histograms by birth month were calculated for the full study population and partitioned by age of the patient at disease onset above and below ten years. These histograms were normalized for the monthly birth rate using US natality data from 1968 to 2011. The fraction of births per month out of the overall total, multiplied by 12, yields monthly weighting factors with a mean of 1 (Table 2). To verify that these weights are representative across all ages, we computed independent weights for each year; the standard deviation for each month was approximately 2%, showing little variation over the 44 years. Using US natality data was assumed to be adequate, given its low variation and the predominant US population in the study.

To test for a seasonal dependence, we applied two independent methods. First, we selected the standard deviation of the natality-adjusted histogram as a test statistic. This method only quantifies the likelihood that the birth months are uniformly distributed throughout the year. Second, a geometric technique was used to establish whether a seasonal dependence was biased toward a part of the year. In this method, the histogram totals are arranged as weights around a circle and the "center of mass" is compared against a chi-squared distribution.

We generated an empirical distribution function of the test statistic by repeatedly drawing an equivalent population (89 patients with first symptoms before the age of ten) from a uniform distribution and computing the standard deviation of the resulting histogram adjusted for the natality weighting factors. The computed p value was 0.003, indicating a statistically significant deviation from a uniform distribution.

This process was repeated for a range of upper age thresholds. In Fig. 1a, b, the sample sizes and p-values are plotted as functions of upper age threshold, showing that the null hypothesis is least likely when considering the patients under the age of ten, as shown by the minimum in Fig. 1b. The rising p value for higher age thresholds indicates that the seasonal dependence seen with the younger population becomes obscured when the older patients are included. The fluctuating p value for age thresholds below five years results from the smaller sample sizes.

Table 1. Summary of case statistics collected.

Total case number:	***n* = 118**	
Sex:	62 female	56 male
Hemisphere:	113 northern	5 southern
Disorder:	115 LCH	3 LCH & HLH

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Table 2. Total number of cases by month (adjusted for hemisphere), total number of births recorded by month in the USA from 1968 to 2011, and corresponding monthly weight (correction factor) to produce the adjusted case number normalized by birth rate.

Month	Number of cases	Number of births	Monthly weight	Adjusted cases
January	11	12,331,961	0.9756	10.73
February	5	11,524,374	0.9117	4.56
March	8	12,674,321	1.0027	8.02
April	9	12,104,321	0.9576	8.62
May	14	12,638,731	0.9999	14.00
June	18	12,557,706	0.9935	17.88
July	14	13,363,513	1.0572	14.80
August	8	13,510,916	1.0689	8.55
September	6	13,240,807	1.0475	6.29
October	11	12,922,262	1.0223	11.25
November	7	12,178,315	0.9635	6.74
December	7	12,636,479	0.9997	7.00

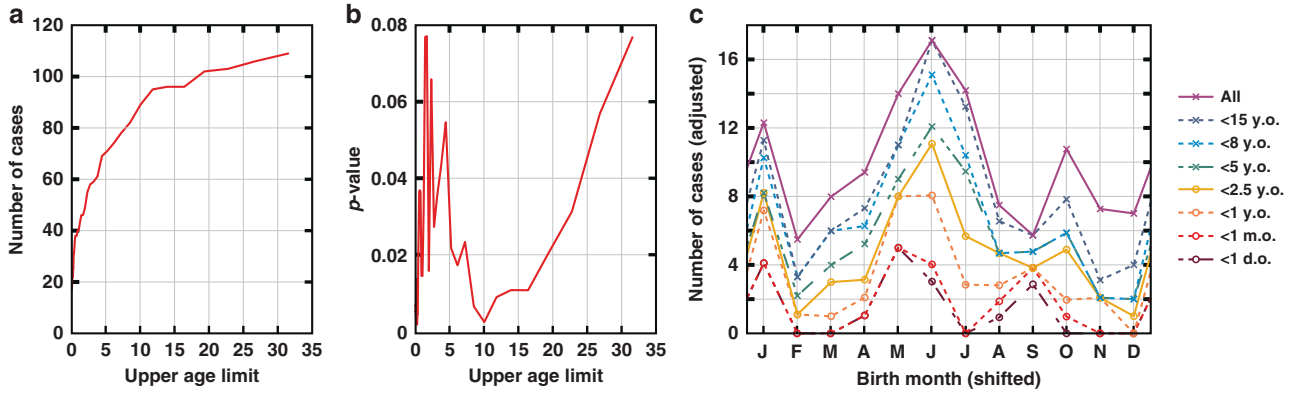

Fig. 1 Analysis of age threshold. a Sample size for the reweighted standard deviation of monthly histograms for Langerhans cell histiocytosis (LCH) cases (age at presentation) filtered using an upper age threshold, and **b** *p* value corresponding to the sample using the same upper age threshold. **c** Histogram of the number of LCH cases binned by birth month using a range of upper age thresholds.

Using the geometric technique for the population of patients diagnosed before the age of ten, the *p* value for the null hypothesis of no seasonal trend is 0.0004, with the seasonal variation peaking in mid-June.

Assuming that the seasonal variation exists, we looked in more detail at the ages where this trend is apparent. In Fig. 1c, we plot cumulative histograms of the birth month for a range of age thresholds to determine at which age of disease onset a seasonal variation may be most pronounced. The strongest contributors to the seasonal variation are the newborns, seen as the dark red line in Fig. 1c; furthermore, the seasonal dependence decreases with patient age.

While the effect of birth month has been linked to risk of autoimmunity, we are not aware of prior studies that have investigated whether the month of birth (as opposed to diagnosis) for only the youngest patients was a risk factor for inflammatory neoplasms, such as LCH. Prior studies have examined the effect of seasonal variation on LCH diagnosis. Stålemark et al. found a seasonal variation in the month of diagnosis with 22 children diagnosed in the fall and winter and only seven in the spring and summer[12], while Chen et al. noted that during 1997–1998 most LCH cases in Taiwan were diagnosed in the summer[13]. In contrast, Alston et al. reported no detection of a significant seasonal trend for month of first symptom, or month of diagnosis, or month of birth, however it does not appear that they separated the patients according to age[14]. These studies were also focused on patients treated at single institutions. We believe the present study is the first to leverage the global nature of social networking to provide a geographically diverse patient population.

The seasonal dependence in the youngest patients suggests a possible environmental factor during pregnancy. In particular, the possibility of a causal correlation with an infection with a seasonal variation may be considered, as well as the role of maternal vitamin D, studied in autoimmune disorders including MS. Studies have shown that infants born in May had lower 25-hydroxyvitamin D than those born in November, attributed to insufficient maternal vitamin D due to low exposure to UVG radiation in autumn and winter[15]. The stronger seasonal dependence in younger patients is consistent with a higher prevalence of severe multi-system LCH in that population.

While the seasonal dependence is not conclusive of an etiology or classification for LCH, we hope that this pilot study can stimulate better understanding on the contributing risk factors for LCH and on differences between the multi-system and single-system forms of LCH. Based on the results here, further analyses of existing patient databases are suggested to study a possible birth month association with developing LCH.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Web-based data where patients provided consent.

ADDITIONAL INFORMATION

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