Differences in Childhood Growth Parameters Between Patients With Somatic and Heritable Retinoblastoma

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PURPOSE. Little is known regarding differences in childhood growth between somatic and heritable retinoblastoma (Rb) populations. We aimed to compare childhood growth parameters between somatic and heritable Rb cohorts at birth and at time of diagnosis with Rb.

METHODS. A multinational, longitudinal cohort study was conducted with patients from 11 centers in 10 countries who presented with treatment naïve Rb from January to December 2019. Variables of interest included age, sex, and size characteristics at birth and at time of presentation, as well as germline mutation status. After Bonferroni correction, results were statistically significant if the *P* value was less than 0.005.

RESULTS. We enrolled 696 patients, with 253 analyzed after exclusion criteria applied. Between somatic ($n = 39$) and heritable ($n = 214$) Rb cohorts, with males and females analyzed separately, there was no significant difference in birth weight percentile, weight percentile at time of diagnosis, length percentile at time of diagnosis, weight-for-length percentile at time of diagnosis, or change of weight percentile from birth to time of diagnosis. Patients with heritable Rb had a smaller mean weight percentile at birth and smaller mean weight and length percentiles at time of diagnosis with Rb, although this difference was not statistically significant. All cohorts experienced a slight negative change of

weight percentile from birth to time of diagnosis. No cohort mean percentiles met criteria for failure to thrive, defined as less than the 5th percentile.

CONCLUSIONS. Children with Rb seem to have normal birth and childhood growth patterns. There is no definitive evidence that somatic or heritable Rb has a biological or environmental impact on childhood growth parameters.

Keywords: retinoblastoma, failure to thrive, germline, childhood growth, growth parameters

Retinoblastoma (Rb) is the most common ocular malignancy in children worldwide, affecting 6000 to 8000 children annually.[1,2] Rb can occur owing to a somatic mutation in one cell, or from a germline mutation resulting in multiple cells with ability to cause disease. Little is known about the effects of this disease on childhood growth and development. Specifically, there is a paucity of data on the effect of Rb on childhood growth parameters, such as height and weight. The limited studies that have been done report mixed findings. It has been reported that there is no difference in height between patients with Rb at time of diagnosis and the general population[3] and that patients with somatic and heritable Rb have no difference in height or weight when compared with each other.[4] It has also been reported that patients with Rb and their siblings weigh more when compared with the general population[4] and that patients with Rb are more likely to be shorter than the general population.[5] All of these studies were conducted with data from a single center or a single country.

The purpose of our study was to investigate the effects of Rb on childhood physical development in a large, multinational cohort by comparing childhood growth parameters between somatic and heritable Rb. To our knowledge this study is the first to encompass an international cohort. The study is much more applicable to the entire global population when compared with the previously mentioned studies. If there are differences in physical childhood growth parameters between patients with somatic and heritable Rb at the time of birth, this finding would suggest strongly that the presence or absence of an Rb mutation influences biological parameters beyond cancer. If there are growth parameter differences between somatic and heritable Rb at the time of presentation with Rb, this factor would suggest biological or environmental differences that may affect physical development. If such factors exist that lead to different outcomes in those with somatic or heritable Rb, it is imperative to understand them so that they can be addressed for the best patient outcomes.

METHODS

A prospective observational study was conducted in Rb centers from 10 different countries. Full details of the methodology are described in detail in Kaliki et al.[6] Briefly, clinical and demographic information were gathered prospectively for all patients with newly diagnosed Rb from January 2019 to December 2019. Centers were selected to span multiple continents and income ranges. The study was approved by the London School of Hygiene & Tropical Medicine Institutional Review Board (reference No. 15882). All participating centers received clearance from their respective institutional review board and ethics

committee. The study adhered to the tenets of Declaration of Helsinki. Informed consent was obtained from all parents or guardians of the children included in the study.

The following variables were assessed in each patient: date of birth, sex, gestational age at birth, birth weight, date of initial presentation at Rb referral center (which is the official date of diagnosis with Rb), patient weight and length on date of presentation to the Rb center, laterality, genetic testing of pathogenic alleles, and family history of Rb. Patients were separated into somatic and heritable Rb cohorts. We considered any patient with bilateral disease, a pathogenic Rb allele, or a family history of Rb to have heritable Rb. Patients with genetic testing negative for a pathogenic Rb allele were considered to have somatic Rb. Unilateral cases with no family history and no genetic testing performed were excluded from analysis. This exclusion was based on the reality that 10% to 15% of patients with unilateral Rb have a pathogenic Rb allele and are heritable cases.[7,8]

Growth Parameter Percentiles

Patients were first separated into preterm and term births. Term birth is defined as a gestational age between 37 and 42 weeks, and preterm birth is a gestational age of less than 37 weeks.[9] There is not one preterm growth standard that is recommended universally or used internationally,[10,11] so all preterm born patients were excluded from birth weight analyses. For term births, the weight at birth was converted to percentiles using the World Health Organization 2006 *Child Growth Standards*,[12] which was created from an international cohort and is used by the vast majority of countries for term births to 5 years old.[13]

Age at presentation to the Rb referral center was calculated by subtracting the date of birth from the date of presentation to the Rb referral center. Age in days was converted to months by using the constant 0.0329 month/days, because this is the quotient of 12 months and 365 days. Once converted to months, age at presentation values were rounded down to the nearest whole number.

For patients born preterm who presented to an Rb referral center at less than 24 months from birth, a corrected age was calculated for use. Corrected age is used routinely for children born prematurely until 24 months after birth, also known as 24 months of chronological age. Before a chronological age of 24 months a prematurely born child is typically delayed in multiple domains including weight and length when compared with their full-term counterparts. Corrected age appropriately accounts for these delays.[14] Corrected age at presentation was calculated first by subtracting the preterm gestational age at birth by a term gestational age of 40 weeks. This difference was then added to the time between date of birth and date of presentation to Rb referral

center. Patients born preterm who presented with Rb with a negative corrected age, that is a corrected age of less than 0 months, were excluded from the presentation analysis.

We used the World Health Organization 2006 *Child Growth Standards*[12] to convert the weight and length of patients who were between 0 and 5 years old on presentation to the Rb referral center to percentiles for weight, length, and weight-for-length. Similar to premature birth growth parameters, there are multiple growth curves for children older than 5 years old, but not one is accepted universally and internationally.[15] Patients older than 5 years of age when they presented with Rb were excluded from growth parameter at presentation analyses.

There are multiple definitions of failure to thrive in the literature.[16,17] We define failure to thrive as length, weight, or weight-for-length less than the 5th percentile for age and sex because this definition is commonly used.

Statistical Analysis

Patients were divided into heritable and somatic cohorts as described elsewhere in this article. Groups were then compared based on sex owing to the different growth curves of males and females. We completed all comparisons between heritable and somatic cohorts with unpaired two-tailed *t* tests. A total of 10 statistical comparisons were made and a Bonferroni correction was applied to reduce type I error. Bonferroni correction is recommended when multiple tests are carried out to test a hypothesis.[18] After Bonferroni correction, results were considered statistically significant if the *P* value was less than 0.005.

RESULTS

A total of 11 Rb centers in 10 countries enrolled a total of 696 patients in the study (Table 1). Of these, one patient was excluded from analysis as no sex was recorded at birth. Another 442 were excluded from analysis because they had unilateral Rb but no family history or genetic testing record. A total of 253 patients had sufficient information to determine heritable or somatic status and were included in the analyses (Table 1), 39 with somatic Rb and 214 with heritable Rb. Of the 253 patients, there was variable recording of weight at birth and of weight and length at time of presentation with Rb (Table 2). Of the analyzable patients, 19 males and 26 females were preterm at birth and excluded from birth weight analysis. Two patients were older than 5 years when they presented with Rb and were excluded

TABLE 1. Distribution of Patients by Rb Referral Center

Country of Rb Referral Center	No. of Patients Enrolled	No. of Patients Analyzed
Bangladesh	136	44
China	166	63
Ethiopia	74	22
France	49	17
India	131	48
Pakistan	30	11
Peru	47	7
Russia	42	26
UK	14	11
USA	7	4

Enrolled *N* = 696. Analyzed *N* = 253.

TABLE 2. Completeness of Data

	Male	Female
Weight recorded at term birth		
Somatic	19	14
Heritable	90	80
Weight recorded at presentation with Rb		
Somatic	19	15
Heritable	111	102
Length recorded at presentation with Rb		
Somatic	14	12
Heritable	96	75
Weight and length recorded at presentation with Rb		
Somatic	14	12
Heritable	96	75
Weight recorded at term birth and at presentation with Rb		
Somatic	17	11
Heritable	90	78

N = 253 patients met the criteria for analysis, of which 39 had somatic Rb and 214 had heritable Rb.
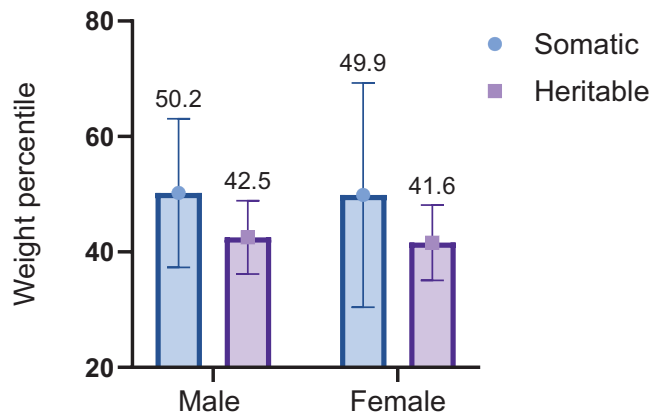

FIGURE 1. Mean weight percentiles at birth. Mean weight percentile at birth was not significantly different between males with somatic and heritable Rb (*P* = 0.31), nor between females with somatic and heritable Rb (*P* = 0.35).

from growth parameter analysis at presentation. The oldest patient at presentation with Rb was 11 years old.

Between somatic and heritable Rb cohorts there was no significant difference in birth weight percentiles in both males (*P* = 0.31) and females (*P* = 0.35) (Fig. 1). At the time of presentation with Rb between somatic and heritable Rb cohorts, there was no significant difference in weight percentiles in either males (*P* = 0.04) or females (*P* = 0.22), in length percentile in either males (*P* = 0.10) or females (*P* = 0.23), or in weight-for length percentile in either males (*P* = 0.78) or females (*P* = 0.84) (Fig. 2). There was no significant difference in change of weight percentile from birth to time of presentation with Rb between somatic and heritable Rb cohorts in males (*P* = 0.52) and females (*P* = 0.52) (Fig. 3). None of the cohort mean percentiles used in the multiple analyses met criteria for failure to thrive.

DISCUSSION

Overall, we found no significant difference between somatic and heritable Rb cohorts in all growth parameter compar-
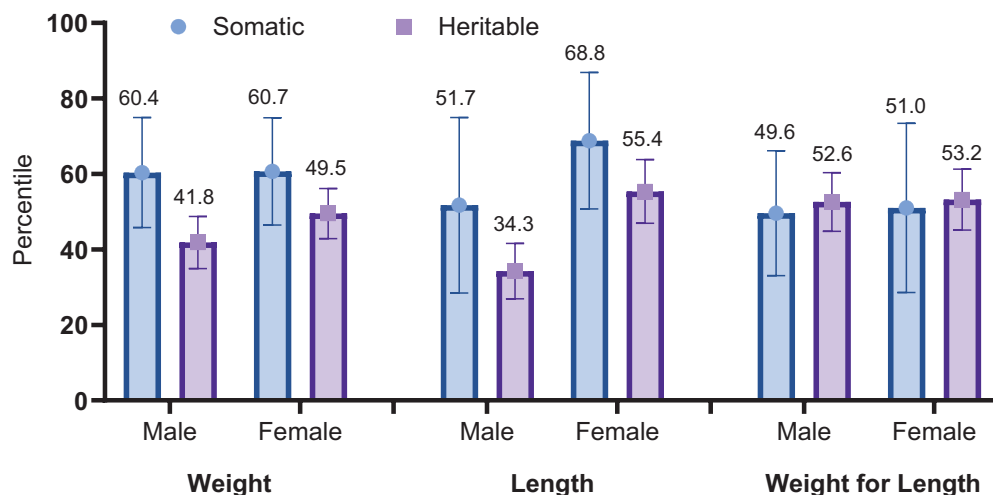
FIGURE 2. Mean weight, length, and weight for length percentiles at time of diagnosis with Rb. At time of diagnosis with Rb, there was no significant difference between males with somatic and heritable Rb in weight ($P = 0.04$), length ($P = 0.10$), or weight-for-length percentile ($P = 0.78$). There was no significant difference between females with somatic and heritable Rb in weight ($P = 0.23$), length ($P = 0.23$), or weight-for-length percentile ($P = 0.84$) at time of diagnosis with Rb.
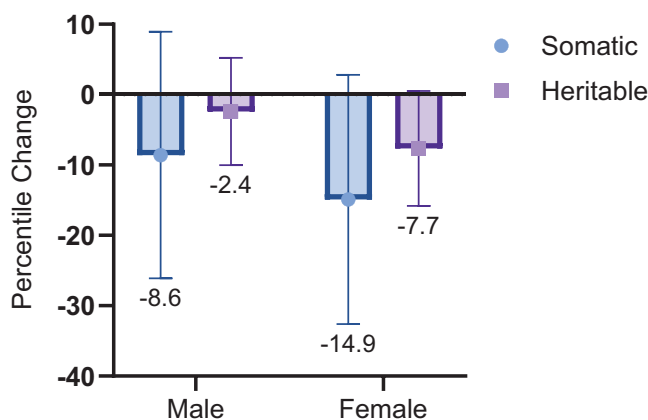

FIGURE 3. Mean change of weight percentile from birth to time of diagnosis with Rb. Mean change of weight percentile from birth to time of diagnosis with Rb was not significantly different between males with somatic and heritable Rb ($P = 0.52$), nor between females with somatic and heritable Rb ($P = 0.52$).

isons at birth and at the time of presentation with Rb. Furthermore, there was no evidence of failure to thrive in any group, somatic or heritable, males or females. The lack of significant differences in birth weight and growth over time in both males and females suggests a lack of biological or environmental factors that affect patients with heritable Rb differently from those with somatic Rb.

Although not statistically significant, there was a consistent trend of heritable cohorts having a smaller mean weight percentile at birth (Fig. 1), a smaller mean weight at presentation with Rb, and a smaller mean length at presentation with Rb when compared with the somatic cohort (Fig. 2). This finding was seen in both males and females. It is possible that, with higher powered studies, we would indeed see a significant difference in growth parameters between sporadic and heritable Rb.

An interesting finding is that the change in mean weight percentile from birth to the time of presentation with Rb was negative in all cohorts (Fig. 3). There was no significant difference between the somatic and the heritable groups. These trends were minimal and did not lead to failure to thrive. Although these small trends may be due to random chance, we cannot rule out the possibility of small effects from environmental factors surrounding the care of children with Rb, such as family stress or frequent and extended travel, taking a toll. This trend cannot be attributed to medical treatment of Rb, such as chemotherapy, because our study end point was time of presentation with Rb, before any medical treatment began.

Previously published data for growth parameters in children with Rb are scarce. Peek et al.[4] observed that patients with somatic and heritable Rb, averaging 4.42 years old, had no differences in height. Their study of the national Dutch population mirrors our findings of an international population. They also found that patients with Rb, with no differentiation made between somatic or heritable disease, were the same height as their Rb unaffected siblings and the age-matched general Dutch population.

Batra et al.[5] found Rb survivors averaging 8 years old were more likely to be shorter than the sex- and age-matched general Indian population. Their study, however, included 121 patients who underwent chemotherapy with only 12 who did not. They found that 31% of chemotherapy-treated patients met criteria for short stature, while only 12% of non–chemotherapy-treated patients met this criteria. A *P* value of 0.09 for this comparison was not statistically significant, but suggests that treatment with chemotherapy could be a potential confounder if further studied.

Yang et al.[19] observed that in 87 patients presenting for intravenous chemotherapy for Rb treatment, there was no significant difference in prechemotherapy height with the age- and sex-matched general Chinese population. Postchemotherapy patients were more likely to be shorter than the matched general population ($P = 0.035$), and those who underwent more than four cycles of chemotherapy had

a larger height deficit than those who underwent four or fewer cycles ($P = 0.008$).

Contrary to these previous studies, our study contained no confounders of treatment, such as previous surgery, anesthesia, or chemotherapy. Only treatment-naïve patients were enrolled in this study. An additional strength of this study is that the data came from an international population spanning 10 different countries across 5 continents, a distinction between previous single center and/or single nation data.[3–5,19]

Limitations to our study include the fact that a large number of enrolled patients were excluded from the analysis because they had no genetic testing recorded in the setting of unilateral Rb without a family history. Without genetic testing recorded in this group, it was impossible to determine if they had sporadic or heritable Rb because 10% to 15% of unilateral cases are heritable.[7,8] If genetic testing records could be obtained for these enrollees and for enrollees in future studies, it would make our study and future studies stronger.

We were limited in our ability to analyze preterm birth weights as well as growth parameters at presentation for patients who presented with Rb older than 5 years of age because there are not universally preferred growth charts for either of these groups. The Fenton[11] and INTER-GROWTH21st[10] growth charts include premature births and were created from different international populations. They produce different results, and a consensus on a recommended growth chart for premature births is lacking.[20–22] Similarly, there are multiple available growth charts for children older than 5 years of age, but not one in particular is widely used internationally.[15] Only two patients were excluded from time of presentation with Rb analysis because of their age being more than 5 years old; however, 45 patients were excluded from birth weight analyses because they were born preterm. The lack of universally accepted growth standards for premature births and children over 5 years of age will continue to be a barrier in studies with international cohorts such as this.

Another limitation is that our data are constrained in their ability to assess growth parameters over time. Failure to thrive has multiple definitions with no single best definition.[16,17] In our study, we defined failure to thrive as length, weight, or weight-for-length at less than the 5th percentile for age and sex. Although this metric is considered accurate by The American Society for Parenteral and Enteral Nutrition, they recommend comparing multiple time points of a growth parameter when available because this strategy is considered even more accurate.[17] Given that we had no more than two data points for each patient's weight over time, weight at birth and at time with presentation of Rb, we were able to provide a dynamic growth measurement for weight with a single trend. The other measured parameters of length and weight-for-length were only provided at the time of presentation with Rb, giving a static picture of these growth parameters.

Despite the limitations, these data represent the largest analysis of growth parameters in children with treatment naïve Rb to date and it is applicable to a global population. The smaller mean weight percentiles at birth and smaller mean weight and length percentiles at presentation with Rb among heritable Rb males and females were not statistically significant, nor were the negative changes in mean weight percentile from birth to time of presentation with Rb in every cohort. Overall, this study demonstrates the welcome finding that children with both somatic and heritable Rb showed normal physical development at birth, as well as normal early childhood growth when compared with each other. There does not seem to be any biological or environmental factors affecting growth and physical development of children with all forms of Rb. Additional studies of treatment-naïve patients with Rb from international populations should be conducted to contribute to understanding how somatic and heritable Rb impact physical growth.

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