Diminished Blood Pressure Profiles in Children With Down Syndrome

Jonathan D. Santoro, Sarah Lee, Michael Mlynash, Elizabeth W. Mayne, Michael S. Rafii, Brian G. Skotko

Abstract—This study sought to analyze blood pressure trends in children with Down syndrome at multiple centers. A multicenter, retrospective, cross-sectional study was performed. All patients were <18 years and had a diagnosis of Down syndrome. Existing comorbidities were nonexclusionary. For each patient, 3 blood pressure recordings were obtained from routine clinic visits. In total, 887 patients with 2661 total blood pressure recordings were included in this study. The average blood pressure percentile for patients was 38.87 with a median percentile of 31.5. Age, sex, and race were not predictive of blood pressure percentile. Compared with established data from the National Heart Lung and Blood Institute and National Health and Nutrition Examination Survey cohort (ages 8–18 years), blood pressure in our Down syndrome population was statistically lower by 6.1 percentile points ($P<0.001$), with the greatest difference at higher blood pressure percentiles ($P<0.001$). Only 10% of all Down syndrome cohort blood pressure recordings were greater than the National Heart Lung and Blood Institute/National Health and Nutrition Examination Survey 70th percentile, with no patients meeting criteria for prehypertension or hypertension. Additional comparisons against American Academy of Pediatrics data were similar and statistically significant. In children with Down syndrome, there is a 12 percentile point reduction in baseline blood pressure compared with age- and height-matched controls reported in the National Heart Lung and Blood Institute/National Health and Nutrition Examination Survey and American Academy of Pediatrics cohorts. This data can potentially be utilized in the evaluation and care of persons with Down syndrome in their pediatric medical homes. (Hypertension. 2020;75:00-00. DOI: 10.1161/HYPERTENSIONAHA.119.14416.)

Key Words: blood pressure ■ Down syndrome ■ genetic predisposition to disease ■ hypertension ■ population health

Down syndrome (DS) is a genetic condition caused by the triplication of chromosome 21. First described by John Langdon Down in 1866, DS is one of the most commonly diagnosed genetic conditions. There are ≈210,000 persons with DS living in the United States with a prevalence of 8.27 persons per 10,000. Persons with DS are at risk for many comorbid medical problems including congenital heart defects, frequent infections, hypothyroidism, sleep disordered breathing, and metabolic dysregulation including obesity, asthma, moyamoya syndrome (MMS), psychiatric conditions, and intellectual disability. Blood pressure (BP) is integral to the diagnosis, monitoring, and management of these diseases. Further, BP can serve as an inexpensive and easy to use biomarker of disease activity or response to therapy and can be used to monitor for vascular side effects of pharmacological interventions, such as hypertension. In some diseases, such as MMS, BP trends can be used to predict impending neurological insult, such as cerebrovascular accident, up to 18 months before disease activity.

In spite of DS being one of the most well described genetic disorders, little is known about BP in this unique population. Historical reports suggest that BP in adults with DS may be lower, although these studies are limited by small sample size, heterogeneous population, and reliance on institutionalized individuals in an era of limited medical intervention. A recent study evaluated BP profiles in children with DS reported baseline BPs to be 12 percentile points lower on average compared with age-matched controls. However, this study was limited by its inclusion of persons with DS with no comorbid medical issues and was regionally restricted, making population-based extrapolations difficult.

This study sought to assess BP profiles in children with DS using a multicenter retrospective chart review with the goal of establishing a groundwork for population-based metrics in this population for use in the pediatric medical home.
Methods

Anonymized data and statistical methodology that support the findings of this study are available from the corresponding author upon reasonable request and IRB authorization.

Patient Selection

Following IRB approval, all patients with DS were identified retrospectively by searching International Classification of Diseases-9 and International Classification of Diseases-10 codes for DS from 6 different clinical practices including 2 tertiary academic centers (Lucile Packard Children’s Hospital at Stanford, Palo Alto, CA and Massachusetts General Hospital, Boston, MA), a large county hospital (Santa Clara County Medical Center, San Jose, CA), and 3 private, primary-care pediatric practices (based in NY, MA, and CA). Patients were included in this study if they were evaluated on at least 3 occasions between 2000 and 2018 and had attainment of height, weight, and blood pressure during each encounter. Patients were excluded if they met any of the following criteria: (1) fewer than 3 BP collections before turning 18 years of age, (2) fewer than 3 well child BP collections, and (3) fewer than 6 months between BP collections. Patients were not excluded for any medical comorbidty, medication use, or prior evaluation in a subspecialty clinic. Selection of patients is displayed in Figure 1.

Blood Pressure Measurement and Conversion to Percentiles

Blood pressure measurements were extracted from clinic notes at each institution, outside clinical records (for patients with transfers of care), and/or pediatrician well child, vaccination only, or urgent clinic visits, which were not expected to be associated with changes in BP. Patients could not be febrile or have an infectious diagnosis as part of the visit for BP extraction. Blood pressure readings obtained during hospitalizations or emergency room encounters were not utilized. Patients admitted to the hospital, following evaluation (even if not considered urgent), were also excluded. As this was a retrospective review, blood pressure measurement methods were not controlled.

To allow comparison across different ages and statures in this population, each BP measurement was converted to percentile for age, height, and sex using standardized data from the National Heart, Lung, and Blood Institute (NHLBI), which was derived from the National Health and Nutrition Examination Survey (NHANES). This was necessary given established growth and height delay in the DS population and inclusion of persons with obesity. The formula for calculation is displayed as an online-only Data Supplement.

The control group was comprised of the NHANES 2001 to 2002 participants who were 18 years old or younger and had BP measured. Only examinees 8 years and older had BP measured in NHANES, and we used their reported average systolic blood pressure. We converted systolic blood pressure for each participant to sex, age, and height-adjusted Z score and percentile using formulas used in the NHANES study. Height Z scores used for these calculations were computed using a SAS program for the 2000 CDC growth charts for ages 0 to <20 years. As an additional statistical comparison performed for quality control, systolic blood pressure for participants from our cohort was converted and compared with sex, age, and height adjusted percentiles of the most recent American Academy of Pediatrics (AAP) report on hypertension and blood pressure standards. Given anticipated lower height values in our cohort, statistical comparison was made by fixing outlier heights defined as outside of 3.09 absolute Z score: we assigned them to correspond to the heights of the 1st and 99th percentiles of the AAP cohort, respectively. Data for patients <2 years were excluded in this calculation due to insufficient data and thus only children aged 2 to 18 years were compared.

Definition of Hypertension

This study utilized NHLBI and AAP standards for the definition of hypertension, defined as BP recordings ≥95th percentile for age and sex. Similarly, prehypertension was defined as BP recordings >90th and <95th percentile.

Statistical Analysis

We compared BP values between groups using Student t-test or ANOVA analysis. Repeated measures of BP were assessed using paired t-test. Linear regression analysis was used to assess associations between BP and continuous variables. We compared proportions of categorical data between groups using χ² test. To assess effect of time on measurements in combination with sex and race factors, we employed General Linear regression analysis with repeated measures. Skewness was calculated to determine the degree of symmetry of distributions. Levene Test for Equality of Variances was used to compare uniformity of BP percentile distributions between cohorts. All test were 2-sided and significance was defined at α=0.05. Statistical analysis was conducted using SAS 9.4 and IBM SPSS Statistics 25.

Results

In total, 1852 patients met initial inclusion criteria, but this cohort was reduced to 887 patients following application of exclusion criteria, contributing a total of 2661 unique BP recordings (Figure 1). Demographics of our cohort are displayed in Table 1. Mean age was 10.5 years (SD: 4.93) with a median of 11.0 years (interquartile range, 7–15). The majority of our cohort was white (74.3%) and male (52%). Most patients were evaluated in academic medical systems (85%) with private practice (11%) and county hospital systems (4%) comprising the minority of clinical encounters.

Distribution of blood pressure percentiles in our cohort is presented in Figure 2. Across all data points, the average...
BP percentile was mean 38.87 (SD ± 20.11). The median BP percentile was 31.5 (interquartile range of 23–53). There was no statistically significant difference in BP percentiles for sex (P = 0.304) nor race (P = 0.117). Repeated BP assessments in the same patient did not differ by timepoint obtained (P = 0.692).

In our cohort, no patients had a mean BP (averaged over 3 recordings) that met criteria for prehypertension or hypertension, as defined for neurotypically developing age-, height-, and sex-matched counterparts. Of 2661 BP recordings, only 14 (0.52%) met criteria for prehypertension, and 12 (0.45%) met criteria for hypertension. No patients had >1 BP recording that met criteria for prehypertension or hypertension. There was no statistically significant impact of age at first recording on BP over time, demonstrating uniform deviations from established percentile scoring in otherwise healthy children at all data collection points. The NHANES cohort with available data to derive systolic BP percentiles and Z scores (n=2544 patients, 7155 BP recordings) was compared against our cohort. Distribution of BP percentiles is presented in Figure 3. The NHANES cohort was older by 2.5 years (P<0.001 [95% CI, 2.1–2.8]), but there were no differences in sex representation between groups (P=0.440). Our cohort’s BP percentiles were significantly lower by 5.5 percentile points (P<0.001 [95% CI, 4.1–7.0]). Only 2.93% of all recordings in the DS cohort were greater than the established 70th percentile for the NHANES cohort; and just 1% were greater than the 80th percentile. Cumulative percentile distributions between these 2 cohorts are represented in Figure 4. In comparison to the AAP cohort, 5 patients (0.6%) had recordings greater than the 90th percentile which was defined as prehypertension in this group and 1 patient (0.1%) had recordings greater than the 95th percentile which was defined as hypertension.

The NHANES data reported a BP percentile distribution that was more evenly distributed than our cohort (Figure 3). This cohort revealed a significantly larger variance in distribution of BP percentile scores (722 versus 236; P<0.001), pointing out to wider spread and more uniform distribution of percentiles in NHANES cohort, while more clustering around the mean in DS cohort. Our cohort’s distribution was somewhat skewed to the left with longer right tail (skewness=0.20). AAP-based percentiles had similar distribution: 40.30±18.23, variance of 332 and skewness of 0.22. Mean differences between BP percentiles in the DS cohort and NHLBI BP percentile are presented in Table 2. Blood pressure percentiles deviated from established normative values more as the percentile range increased. At the established NHANES 25th percentile, mean BP percentile differed from established norms by only −1 percentile point, but this increased to −12 percentile points at the 50th percentile, −22 percentile points at the 75th percentile, −24 percentile points at the 90th percentile, and −21 percentile points at the 95th percentile points (P<0.001). These differences were preserved by age and were not statistically different between specific ages at diagnosis nor clustered groupings (1 to <6 years, 6 to <13 years, and 13–18 years).
Given the skewed distribution of our data and the need to standardize our measurements, t-scores and z-scores were calculated (online-only Data Supplement). Nearly all patients in the DS cohort fell within 1 SD of the mean due to a prominent skew towards lower BP percentile values. The differences between Z scores were similarly statistically significant by 0.14 ($P<0.001; [95\% CI, 0.09–0.19])

As the NHANES group only included patients ≥8 years of age, we ran sensitivity analysis by restricting our DS cohort on the same youngest age: 612 patients with 1836 BP recordings. The NHANES cohort was slightly younger by 0.25 years ($P=0.072; [95\% CI, −0.02 to 0.52])$, otherwise all other comparisons were similar to the full cohort analysis. There were no differences in sex representation between groups ($P=0.828$).

DS cohort’s BP percentiles were similarly significantly lower by 6.1 percentile points ($P<0.001; [95\% CI, 4.4–7.7])$ and Z scores were lower by 0.16 ($P<0.001; [95\% CI, 0.11–0.21])$.

The mean BP percentiles for AAP and NHANES were not significantly different by 1 or more points (H0=1): mean difference, 1.43 ($95\% CI, 0.97–1.87$), $P=0.065$, indicating that the percentiles by both methods were comparable.

**Discussion**

Our study presents multicenter data demonstrating a statistically significant difference between pediatric-aged persons with DS and their neurotypically age, height, and sex-matched counterparts from the NHLBI and AAP data. These findings are consistent with data previously published in a smaller, regional study on BP in persons with DS. To date, this is the largest cohort of persons with DS ever analyzed, to our knowledge, for BP trends and has the potential to serve as a basis for population-based BP metrics.

The findings of our study are particularly important for accurate interpretation of BP in the DS population given the frequency of medical comorbidities that can alter these findings. Clinicians treating disorders such as hypothyroidism, obstructive sleep apnea and sleep disordered breathing, leukemia, congenital cardiac anomalies, and MMS can use BP trends as an adjunct biomarker of disease presence, response to intervention, and side effect monitoring from procedural or pharmacological interventions. For certain conditions such as cardiac anomalies and sleep disordered breathing, failure to recognize relative changes in BP may lead to cardiovascular dysfunction. While many of these conditions may be reversible or treatable, others such as cerebrovascular accident associated with MMS are not. Prior studies have identified that relative BP elevations may occur up to 18 months before diagnosis of MMS, allowing a window for medical or surgical intervention before cerebrovascular accident in this specific group of persons with both DS and MMS.

The cause of the BP differences between patients with DS and the neurotypical population is unclear. Persons with DS have been previously reported to have aberrant cardiovascular function, even in the absence of congenital heart disease. One hypothesized explanation for these findings include baseline sympathetic dysautonomia, which has been observed in the form of blunted heart rate and blood pressure responses to tilt-table testing. Interestingly, this has also been observed historically in the context of diminished white coat hypertension in the DS population. These findings have also been noted in persons with other intellectual disabilities during short durations of exercise, raising the possibility of physical deconditioning as the driving factor behind these changes; however, this would not account fully for lower resting BP profiles. Specifically, physical deconditioning would be more likely to be associated with blunted adrenergic responsiveness (as observed in sympathetic dysautonomia), resulting in orthostatic hypotension as opposed to resting BP differences, which would not be reliant on autonomic response integrity.

Endovascular structural differences in persons with DS may also contribute to lower baseline BP compared with the general population. Persons with DS are known to have impaired lipid metabolism compared with age-matched controls, yielding higher rates of obesity and metabolic syndrome. While these factors would typically be thought of as contributory to endovascular disease, a large study of persons with DS in the community setting demonstrated that intimal media thickness in the carotid artery was decreased
Table 2. Average Differences in Percentiles Between DS Cohort and Standardized NHLBI Percentiles

<table>
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<th>Age</th>
<th>N</th>
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<th>50th Percentile Δ</th>
<th>75th Percentile Δ</th>
<th>90th Percentile Δ</th>
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Δ indicates difference between DS cohort percentile and standardized NHLBI percentile; BP, blood pressure; DS, Down syndrome; and NHLBI, National Heart, Lung, and Blood Institute.

compared with age-matched controls.\textsuperscript{5} It is plausible that diminished BP profiles in persons with DS may account for these vascular findings and potentially lower rates of atherosclerosis although this is likely polyfactorial and involves genetic, inflammatory, and cardiovascular contributions.\textsuperscript{36} Additionally, high rates of hypothyroidism in the DS population may also predispose to lower BP although the authors would not suspect such a dramatic drop in BP in such a large cohort, particularly since the overwhelming majority of hypothyroidism in this population is medically treated.\textsuperscript{37,38}

There are limitations to the data presented in this study. First, our study is a retrospective, chart-based review. Second, our results might not generalize to the entire DS population. The large majority of patients in our study was evaluated at tertiary pediatric hospitals systems or affiliated clinics, which might represent a more medically complex cohort in comparison to the generalized population with DS. As this was the first large-scale study of BP in the DS population, the authors opted to view all patients blindly without context of comorbid disease so as to best reflect a typical patient with DS presenting to an outpatient clinic. Right now, however, there are no population-based databases for the DS community, so the authors chose to utilize a large cohort across ages, ethnicities, races, geographic locations, and medical settings to gather quality data. BP is a variable biomarker that can be influenced by innumerable factors. We attempted to control for this by obtaining 3 unique recordings per patient and excluding encounters where patients were ill. Additional studies are planned to subanalyze patients with comorbid disease, specifically with those with congenital cardiac disease, obstructive sleep apnea, and hypothyroidism. For comparison, the NHLBI/NHANES cohort was used as the preferential comparative cohort given its inclusion of children with obesity, which is prevalent in the DS population. However, this cohort included mostly older patients who were aged 8 years or older. The authors controlled for this by comparing this group to a subpopulation of our cohort that was age-matched and by performing a second analysis comparing our data to the AAP cohort from 2017 although these data were unable to be directly compared and thus was assessed for clinical skew instead. In either case, both data sets revealed that our cohort was equally around the 39th percentile in both groups with a heavy skew toward the mean and lower blood pressures. Similarly, the use of height-matched healthy controls may have skewed the comparative value of our findings as children with DS are established to be shorter than age-matched peers. For this reason, 28% of our DS cohort was height-matched to children <5th percentile for age. This may increase the chance of comparing our
DS cohort to children with other health issues which predispose to or cause shorter stature. The cause of BP abnormalities was not assessed in this study but warrants further investigation, specifically with regard to identifying the contribution of physical deconditioning to these observations. Finally, our study population includes patients that may have gone on to develop a co-occurring condition (such as obstructive sleep apnea), which may also falsely elevate BP recordings in this cohort. This may be further compounded by the fact that the majority of patients were evaluated at tertiary academic centers which could induce a severity bias due to presumably higher medical complexity.

Perspectives

We found that children with DS have significantly lower BP compared with established BP percentiles from a large national cohort. Creating reference BP values tailored specifically to children with DS has the potential to significantly improve screening and detection of serious medical conditions, which in turn could reduce hospitalizations, increase lifespan, and improve overall quality of life. These data could potentially lead to an improved ability for pediatricians to screen for harmful pathology in patients with DS by use of our raw data, t-scores, and Z-scores. The authors think that our ability to provide a more personalized approach to medical care in this at-risk population is important and could lead to improved quality of medical care. Future studies interrogating the successful screening of persons with DS for medical conditions (such as MMS) using our data set is a logical next step based on the results of our study.

Conclusions

In pediatric-aged patients with DS, there is a 12 percentile point reduction in baseline BP compared with age- and height-matched controls as reported in the standard NHLBI/NHANES and AAP cohorts. These data can be utilized in the evaluation and care of persons with DS in their pediatric medical homes and can provide a framework for clinical decision-making although future prospective and standardized studies are needed.

Sources of Funding

None.

Disclosures

B.G. Skotko occasionally consults on the topic of Down syndrome through Gerson Lehman Group. He receives remuneration from Down syndrome nonprofit organizations for speaking engagements and associated travel expenses. B.G. Skotko receives annual royalties from Woodbine House, Inc, for the publication of his book, Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters. Within the past 2 years, he has received research funding from F. Hoffmann-La Roche, Inc and LuMind IDSC Research Foundation to conduct clinical trials for people with Down syndrome. B.G. Skotko is occasionally asked to serve as an expert witness for legal cases where Down syndrome is discussed. The other authors report no conflicts.

References


Novelty and Significance

What Is New?
- This study is the first ever multicenter assessment of blood pressure in persons with Down syndrome.

What Is Relevant?
- While Down syndrome clinical care is an area of rich research, blood pressure profiling in this population is limited to small, heterogeneous, studies. The normalized blood pressure ranges for children with Down syndrome are unknown.

Summary

This is the first multicenter study of blood pressure profiling in children with Down syndrome. We found that children with Down syndrome have a 12-percentile points difference in mean blood pressure compared with healthy controls.