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ORIGINAL RESEARCH ARTICLE

Prematurity and Delayed Diagnosis of Down Syndrome

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ABSTRACT

OBJECTIVE: The aim of this study was to compare age at diagnosis of common aneuploidies with gestational age (GA) at birth to determine whether prematurity is associated with delayed diagnosis.

METHODS: We conducted a retrospective cohort study of neonates with Patau syndrome (PS), Edwards syndrome (ES), or Down syndrome (DS) admitted to any Nationwide Children's Hospital neonatal intensive care unit (NICU) from 2010 to 2021. The exposure of interest was birth GA: less than 34 weeks, 34 to 36 weeks, and 37 weeks or more. Age at diagnosis for PS/ES and DS was compared between GA groups using the Jonckheere-Terpstra rank-based nonparametric test for ordered alternatives.

RESULTS: Among neonates with PS/ES, the median age (days) at karyotypic diagnosis for preterm, late-preterm, and term/postterm neonates was 3 (IQR, 2–7), 4 (IQR, 3–9), and 3 (IQR, 3–5) days, respectively (trend not significant). Among neonates with DS, the median age (days) at karyotypic diagnosis for preterm, late-preterm, and term/postterm neonates was 6 (IQR, 5–10), 5 (IQR, 3–7), and 4 (IQR, 3–5) days, respectively. The trend of increasing age at diagnosis with increasing prematurity was significant ($P < .01$).

CONCLUSION: Increasing prematurity was associated with increasing age at diagnosis of DS but not PS/ES in a large network of level III/IV NICUs.

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Dr Messick was responsible for study conceptualization, data curation, investigation, formal analysis, validation, data visualization, writing of original manuscript draft, and writing—review and editing. Dr Antoniou was responsible for data curation, formal analysis, investigation, methodology, software, data visualization, and writing—review and editing. Dr Chaudhari was responsible for study conceptualization, data curation, funding acquisition, investigation, methodology design, project administration, resources, supervision, and writing—review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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WHAT'S KNOWN ON THIS SUBJECT: Early diagnosis of genetic disorders has the potential to enable changes in management strategies and improve outcomes, particularly in acute care settings. However, few educational sources include images that couple dysmorphology with prematurity.

WHAT THIS STUDY ADDS: Increasing prematurity was associated with increasing age at diagnosis of Down syndrome but not Patau syndrome or Edwards syndrome. It is plausible that this effect of prematurity on delayed diagnosis impacts a range of other less recognizable genetic syndromes.

Introduction

Patau syndrome (PS), Edwards syndrome (ES), and Down syndrome (DS) are the most common autosomal aneuploidies at birth.[1] Adoption of noninvasive prenatal screening (NIPT) for aneuploidy has increased over the past decade, accompanied by increasing numbers of cases detected antenatally.[2] For those not recognized antenatally, however, postnatal phenotypic recognition is an important factor in timely diagnosis. Early genetic diagnosis has the potential to allow for changes in management strategy and improve outcomes, particularly in acute care settings.[3] Because of the historical lack of diversity in educational materials,[4] new atlases representing diverse populations with malformation syndromes are now available.[5] However, few images couple dysmorphology with prematurity. We hypothesized prematurity would not affect the age at karyotypic diagnosis for PS or ES but might for DS, as the former are associated with more severe and readily apparent anomalies.

Methods

The Nationwide Children's Hospital (NCH) Neonatal Network comprises 7 level III neonatal intensive care units (NICUs) and 1 level IV NICU caring for more than 3000 babies per year. Records of neonates admitted to any NCH NICU from 2010 to 2021 were requested from the NCH's Research Data Warehouse (RDW), including demographic data, clinical note text, and laboratory testing history. This study was approved by the NCH institutional review board (STUDY00000276). Based on the data available October 10, 2022, diagnosis of PS, ES, or DS was established by mining free text in clinical notes and diagnosis codes (*International Classification of Disease* [*ICD*]*-9* and *ICD-10*). All NICU history and physical examination notes for participants were searched using medspaCy in Python with regular expressions to case-insensitively match the following patterns: "t21", "tri[.]* 21", and "down[\']?[s]? syndrome" with similar patterns used to identify cases of PS and ES.[6] This preliminary effort to identify cases of PS/ES/DS was followed by confirmation via manual medical record review by a physician (B.P.C. or E.A.M.). Manual review included determination of participant age at the time of karyotypic diagnosis. The age reported reflects the infant's age at the time karyotype results (including preliminary findings) became available. At our institution, rapid karyotyping is routinely performed, with preliminary results typically reported to the clinical team within an average of 48 hours. Turnaround times may be slightly prolonged for specimens processed over the weekend or when the test is not ordered as statim (STAT). Within our NICU network, clinicians are encouraged to request all karyotypes as STAT to facilitate timely diagnosis. We excluded neonates with documented antenatal suspicion of PS, ES, or DS (from screening laboratory tests or ultrasonography findings) or confirmed diagnosis present on admission (either from antenatal diagnosis or from a postnatal diagnosis obtained at an outside facility prior to transfer to an NCH NICU). Race (Black or African American, white, Asian, multiple race, other, or unknown) was documented as recorded in the RDW (which was, in turn, derived from clinician-assigned information in the electronic health record). Diagnoses of PS/ES were analyzed together, as we hypothesized that the marked dysmorphology associated with these conditions would render age at diagnosis less likely to be impacted by prematurity than DS. The primary exposure was completed weeks gestational age (GA) at birth: less than 34 weeks (preterm), 34 to 36 weeks (late preterm), and 37 weeks or more (term/postterm). Data on the primary exposure were complete. The primary outcome of age at diagnosis was compared between GA groups for PS/ES and for DS using the Jonckheere-Terpstra rank-based nonparametric test for ordered alternatives and between race categories (white vs nonwhite) using Mann-Whitney U test. Race was stratified in this manner because of the historical lack of images of nonwhite participants in training materials. Distribution of race by GA group was also examined to address the potential confounding factor of overall higher risk of preterm birth seen in non-Hispanic Black mothers.[7] Unknown race was not imputed; rather the analyses with race used complete data only. Both for this reason and because of small numbers, no multivariate analyses or regressions were performed.

Results

Of 33 315 NICU admissions born between 2010 and 2021, 29 neonates with PS/ES and 111 neonates with DS met criteria for analysis (Figure 1). Among neonates with PS/ES, the median age (days) at karyotypic diagnosis for preterm, late-preterm, and term/postterm neonates was 3 (IQR, 2–7), 4 (IQR, 3–9), and 3 (IQR, 3–5) days, respectively (trend not significant). Among neonates with DS, the median age at karyotypic diagnosis for preterm, late-preterm, and term/postterm neonates was 6 (IQR, 5–10), 5 (IQR, 3–7), and 4 (IQR, 3–5) days, respectively. The trend of increasing age at diagnosis with increasing prematurity was significant ($P < .01$; Figure 2).

After excluding "unknown" race, race data were available for 95% (n = 105) of infants with DS and 79% (n = 23) of infants with PS/ES. The percentage of nonwhite race participants with DS was 25% (n = 3), 30% (n = 6), and 29% (n = 21) in the preterm, late-preterm, and term groups, respectively. For the participants with PS/ES, 40% (n = 2), 17% (n = 1), and 25% (n = 3) of the preterm, late-preterm, and term participants were nonwhite, respectively. There was not an association of race with prematurity in patients with DS or PS/ES. The median time to diagnosis for white and nonwhite neonates was similar for DS (5 [IQR, 3–6] vs 4 [IQR, 3–5] days; $P = .288$) and PS/ES (3 [IQR, 3–6] vs 4 [IQR, 1–6] days; $P = .895$).

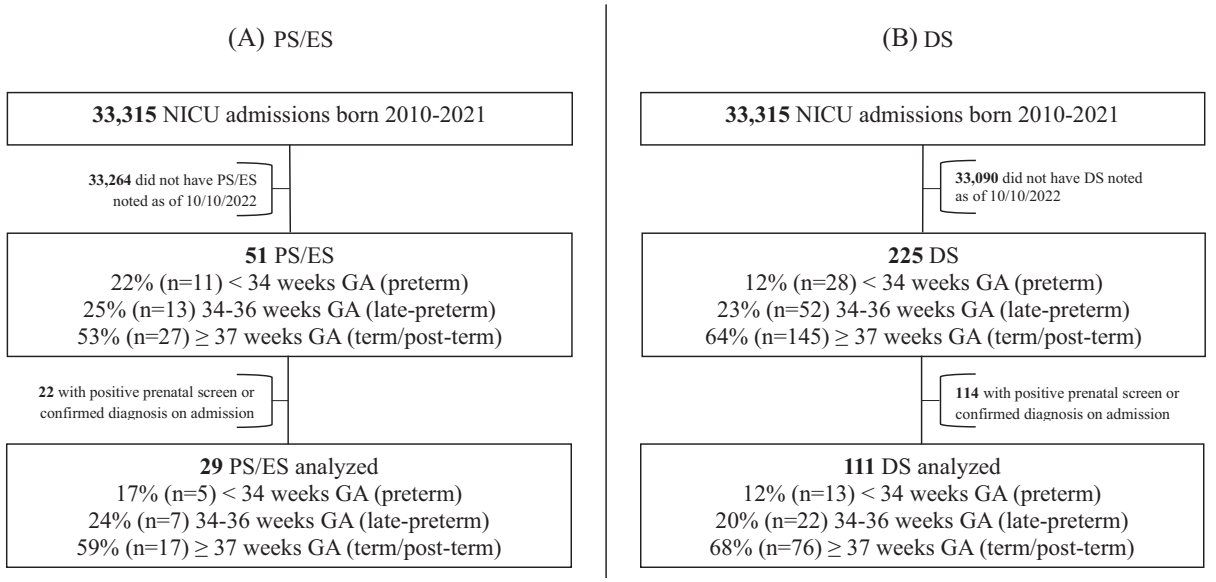

FIGURE 1. Study flow diagram. (A) Ascertainment of participants with PS/ES and (B) ascertainment of participants with DS. Abbreviations: DS, Down syndrome; ES, Edwards syndrome; GA, gestational age; NICU, neonatal intensive care unit; PS, Patau syndrome.

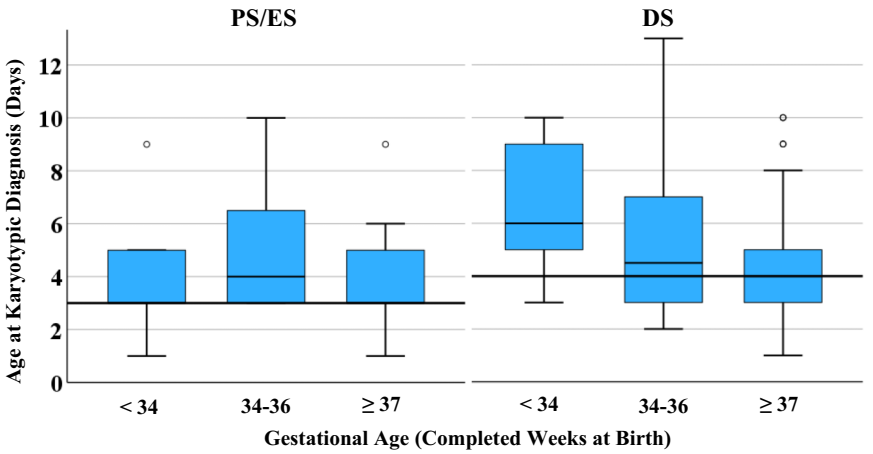

FIGURE 2. Age at karyotypic diagnosis in days by gestational age (GA) for Patau/Edwards syndrome (PS/ES) and Down syndrome (DS). Boxplot illustrating age at diagnosis by GA category for PS/ES (left) and DS (right). *x*-Axis depicts GA groups defined by completed weeks of gestation at birth (preterm, late preterm, term/postterm). *y*-Axis represents age at diagnosis in days. Median age at diagnosis within each GA group is represented by black line within each box. Overall median age at diagnosis for PS/ES and DS, respectively, depicted by dark line intersecting all 3 boxes. Outliers denoted by open circles. Extreme outliers are not depicted to preserve readability. There were no extreme outliers in the PS/ES group. There were 2 extreme outliers amongst preterm infants with DS (68 and 85 d) and 2 extreme outliers amongst term/postterm infants with DS (17 and 31 d). Trend between GA groups for each diagnosis compared using independent-samples Jonckheere-Terpstra test for ordered alternatives (PS/ES $P = .77$, DS $P < .01$).

Discussion

Recently, an important focus has developed on expanding access to educational images of individuals from diverse populations to aid in diagnosis of genetic conditions.[5] However, these atlases lack images of premature infants. As our study demonstrates, prematurity can add another layer of difficulty in establishing a genetic diagnosis when phenotypic recognition is necessary.

While our sample size precluded multivariate analysis, we did not observe a higher percentage of nonwhite infants with increasing prematurity, suggesting that the effect of prematurity we describe is not confounded by race. Subtle facial features associated with a genetic diagnosis such as DS are presumably more difficult to identify in premature infants given the baseline differences in characteristics that are often combined with

respiratory support apparatuses obstructing the face and possibly leading to edema.[8]

A major strength of our study is access to complete neonatal medical records for a large number of neonates born at multiple facilities, representing a near-complete geographically defined cohort of births. In our cohort, genetics consultation was rarely obtained prior to initiation of karyotype testing. Because testing was typically ordered directly by the NICU team, the timing of diagnostic evaluation was not prolonged by awaiting a genetics consult, and, therefore, the reported time to diagnosis was not skewed by consult-related delays. Previous descriptions of the epidemiology of classic aneuploidies in NICUs have not been able to link patient-level characteristics with laboratory results at a granular-enough level to demonstrate these findings.[9–12]

Our study also has several limitations that should be considered. Because our exposure of interest was prematurity, we limited analysis to participants admitted to the NICU. Thus, our findings cannot be extrapolated to neonates cared for in well-baby nurseries. Additionally, despite evaluating more than 33 000 NICU admissions, the number of participants meeting inclusion and exclusion criteria remained small, both because these diagnoses are not common and because many cases were suspected antenatally. We propose that while increasing antenatal detection of aneuploidies through noninvasive screening may reduce the absolute number of patients with PS, ES, or DS admitted to NICUs without antenatal suspicion or diagnosis, neonatologists' reliance on antenatal detection may exacerbate the disparity our study has identified. We were also unable to reliably determine when the team first suspected aneuploidy and subsequently assumed they had the diagnosis prior to karyotype result. While some clinical notes alluded to when the diagnosis of DS was first suspected, the levels of detail and consistency across documentation were variable, limiting our ability to systematically capture this information. We recognize that in the acute NICU setting, timely confirmation of PS or ES is generally prioritized due to its more immediate implications for goals of care discussions. In contrast, for DS, there may have been instances—particularly in the setting of prematurity or other complex medical conditions—wherein clinical suspicion existed earlier, but confirmatory testing was delayed. Unfortunately, this nuance was difficult to reliably quantify from the available records. Additionally, although most of the cases excluded from our study because of prenatal suspicion or diagnosis were primarily identified through NIPT, because of limitations in the available maternal clinical information, we cannot definitively determine whether serum testing or NIPT was pursued in response to abnormal ultrasonography findings. Therefore, we cannot confirm whether these prenatally identified cases exhibited more overt or subtle phenotypic features compared with those diagnosed postnatally. Any disparity by degree of prematurity may be further exacerbated by continued advances in neonatology that move the threshold of viability to lower and lower GA. Because of the sparseness of data, we did not evaluate secular trends and, so, cannot speculate as to whether the disparity we described is changing over time. Lastly, while our study included data from infants admitted to a large network of NICUs across Ohio, which provides a broad and diverse clinical sample, we believe our data are generalizable to similar NICU populations in other regions but may not capture the full range of outcomes seen across all care settings.

In conclusion, increasing prematurity was associated with increasing age at diagnosis of DS but not PS/ES in a large network of level III/IV NICUs. Longer time to diagnosis could delay appropriate medical care, genetic counseling, and psychosocial support. For example, failure to recognize the contribution of hypotonia to respiratory insufficiency may complicate ventilatory management and obscure the rationale for why a preterm infant requires more support than typically expected for GA. In our cohort, while systematic capture of such nuances was limited, delayed recognition of DS could have influenced clinical decision-making and communication with families regarding prognosis and care needs. While delays in diagnosis of 1 to 2 days with increases in prematurity may seem trivial, it is important to consider that the degree of critical illness increases nonlinearly with increasing prematurity, making access to timely diagnosis more valuable to patients, families, and medical care teams. Also, the IQR grew with increasing degrees of prematurity for the participants with DS, such that one-quarter of preterm participants with DS received a karyotypic diagnosis after 10 days of life.

Importantly, it is plausible that this effect of prematurity on delayed diagnosis impacts a range of other less recognizable genetic syndromes. We recommend that genetics training materials include pictures of premature infants when possible. We also note that major studies of genetic testing in NICUs have historically excluded most premature infants by protocol or by limiting eligibility to children with a suspected genetic condition.[13] Future studies should seek to develop the evidence base for genetic testing in premature infants in NICUs. Neonatologists and medical geneticists should recognize that preterm infants in NICUs are at risk of genetic disorders and that such diagnoses may have a material impact on care and counseling in the NICU.

Abbreviations

DS: Down syndrome
ES: Edwards syndrome
GA: gestational age
ICD: International Classification of Disease
NCH: Nationwide Children's Hospital
NICU: neonatal intensive care unit
NIPT: noninvasive prenatal screening

PS: Patau syndrome
RDW: Research Data Warehouse
STAT: signal transducer and activator of transcription

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