Preterm Infant's Heart Rate Variability Near Birth Predicts Autonomic Symptoms at Age 3 to 5 Years

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Abstract

Aims To describe the autonomic function of premature infants born between 28 and 32 weeks of gestation, without medical risk factors, at the age of 3 to 5 years and to assess whether it's possible to predict the appearance of autonomic deficits in these children at this age range.

Methods This follow-up study included 40 out of 55 premature infants born between weeks 28 and 32 during 2018 to 2020. During 2022 to 2023 parents were asked to report on medical and developmental follow-up and treatment, functional characteristics of the autonomic system, and the age at which walking was achieved.

Results Approximately 27% of the participants (11 out of 40) presented autonomic symptoms at 3 to 5 years of age. A predictive relationship was noted between the function of the heart rate control system near birth and the presence of autonomic dysfunctions at ages 3 to 5. Fourteen of 40 children received neurodevelopmental treatments. However, children with autonomic symptoms were not treated for their symptoms.

Conclusion These preliminary findings provide valuable insights into the autonomic function of children born premature and the potential predictive relationship between early autonomic measures and later autonomic dysfunctions. It also highlights the need for increased awareness and intervention strategies for addressing autonomic issues in premature infants to support their overall well-being.

Keywords
- preterm
- autonomic symptoms
- follow-up
- heart rate variability

Introduction

Premature is an infant born before the 37th week of gestation. Approximately 10% of all newborns are premature.[1] Prematurity is a risk factor for developmental disabilities in childhood and adulthood.[2]

The second half of pregnancy and the early neonatal periods are critical for the autonomic nervous system (ANS) maturation.[3] The development of the sympathetic nervous system (SNS) occurs steadily throughout gestation, while the myelinated vagus has accelerated maturation periods, between 25 and 32 weeks of gestation and around 37 to 38 weeks.[3] At birth, the ANS plays a vital role in transitioning from the fetal to the extrauterine environment.[4] Therefore, premature birth has two essential consequences for the development of the ANS: an autonomic system that is not sufficiently developed and, thus, immature to support the physiological changes at birth and in the extrauterine environment. Second, the ANS's continued development occurs in an extrauterine climate, which is not the natural environment for its development.[4]

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Heart rate variability (HRV) is a tool for quantifying and studying ANS tone and measures sympathetic and parasympathetic function.[5] Since the parasympathetic tone is not sufficiently developed in fetuses and premature infants, the sympathetic tone is dominant and expressed in heart rate (HR), HRV, and blood pressure. HRV indices were significantly lower in premature babies evaluated at their term equivalent age as full-term newborns.[6] Preterm infants born between 35 and 38 weeks (gestation age [GA]) show immature cardiac autonomic regulation at birth and a reduced maturation 1 month after delivery, compared with term infants.[7]

The long-term autonomic disorder and symptom impact were subject to a broad literature review. Cross-sectional studies examined HRV indices in children and adults born prematurely. They found that the variability indices are low and that HR recovery after exercise is lower than in their peers born on time, thus pointing to a possible future risk factor for cardiac morbidity.[8,9] No studies examined the findings of autonomic symptoms such as constipation, cold limbs, pain, and sleep disorders in children born prematurely were found. These autonomic disorders are associated with decreased quality of life and daily functioning.[10]

The purpose of this work is to continue a follow-up study conducted on premature infants born at 28 to 32 weeks during 2018 to 2020 and reassess them at the age of 3 to 5 years to:

- Describe the autonomic symptoms at 3 to 5 years of age.
- Examine the predictive ability of the HRV index as taken at the birth age of a premature infant for autonomic system dysfunction at the age of 3 to 5 years. The goal of this identification is early intervention (before the age of 3), which will reduce the severity of the long-term impairments in this system.

Methods

Participants

This secondary follow-up study included 40 out of 55 premature infants born between weeks 28 and 32 during 2018 to 2020 in "Shaare-Zedek" Hospital in Jerusalem, Israel. The study participants do not include premature babies with significant intraventricular hemorrhage (Grade III–IV), clinically significant patent ductus arteriosus, major congenital abnormalities, lung disease requiring respiratory stimulant medication, or sepsis.

Tools

Outcome Measure

Parental Autonomic Questionnaire—During the follow-up phase, the parents were asked about the prevalence and frequency of signs related to their child's autonomic control system dysfunction, including limb temperature, pain, sleep problems, and constipation. The questions are related to the prevalence, duration, and frequency of the appearance of the signs.[11]

Database

The database included in the current study contained the week of birth, weight at birth, Apgar score at 5 and 10 minutes' postdelivery, length of stay in the neonatal intensive care unit (NICU), and 24-hour HRV frequency parameters of the premature infants at the week of birth and week 32.

Procedure

The Ethics Committee of the "Shaare Zedek" Hospital (285-21 SZMP) and the of Tel Aviv University approved the study. After that, a letter was sent to the families where the study goals were presented and a notice that the first authors would contact them. After that, a phone call took place in which the parents were asked to report on medical and developmental follow-up and treatment, functional characteristics of the autonomic system, and the age at which walking was achieved. The information was combined with the database file upon completion of the data collection. The data included infant RR intervals and vital signs monitored via the VitaLogik 6000 Series monitor, which provide electrocardiogram data sampled at 1000 Hz. HRV indices included the frequency domain measures: the high frequency (assessed at band 0.4–2 Hz) mediated by the para-SNS, influenced by the respiratory rate. The SNS and para-SNS mediate the low frequency (LF) power and reflect the baroreflex function. The exact physiological mechanism associated with the very low frequency (VLF) is debated. Whether it is mediated more by the sympathetic or parasympathetic system, it seems to reflect the renin–aldosterone system's activity, temperature regulation, and vascular activity.

Sample Size Calculation

The sample size calculation was based on the findings of previous works,[8,9] which describe autonomic impairment in young and adult people born prematurely. The caution assumption was that there is a moderately strong association ($r = 0.4$–0.5) between autonomic impairment near birth as present by HRV indices that were taken near birth and impaired autonomic system functions during follow-up. According to the accepted determinations of a type 1 error of 5% and a power of 80%, the sample size needed is approximately 40 children.

Statistical Methods

Participants' characteristics were presented using frequency and relative frequency for nominal variables and median and range for ordinal and ratio variables. The differences in the HRV measured near birth between children with or without autonomic symptoms at ages 3 to 5 were assessed by the Mann–Whitney U test. HRV, measured near birth, was evaluated using the receiver operating characteristic (ROC) curve to predict autonomic function at 3 to 5 years with Cramér's association measure. The data analysis was done with the SPSS 25 software, a test defined as significant for $p < 0.05$.

Results

The children in the current study were born prematurely (28–32 weeks of GA) during 2018 to 2020. The median birth age was 31 weeks, and the median Apgar score was 9 at minute 5 (range: 2–9) and 9 at minute 10 (range: 5–9).

The length of stay in the NICU for 30 children for whom this information was available was 41 days (15–96; ►**Table 1**).

In 2022, the first author (N.Z.) called the parents and asked them to report on medical and developmental follow-up and treatment, functional characteristics of the autonomic system, and the age at which their child started to walk. The report mainly was received from the mother (82.5%, $N = 33$), a minority from the father (7.5%, $N = 3$), or both parents together (10%, $N = 4$).

The children were at the median age of 4 years and 3 months, ranging from 2 and 9 months to 5 and 6 months. There was one quadruplet, one triplet, and nine pairs of twins. The median age to achieve walking was 16 months (range: 10–24).

The study's first aim is to describe the autonomic function of infants born at 28 to 32 weeks of gestation at 3 to 5 years of age. Eleven participants had autonomic symptoms, and one participant had two symptoms. The most common sign was sleep problems (►**Table 1**). No significant differences in week birth, weight, and Apgar 5 and 10 were noted between children with and without autonomic symptoms at 3 to 5 years of age.

For 36 children in the sample, HRV values were found from the week of birth and the 32nd week and are present in ►**Table 2**. The data are present for the total sample and is stratified according to findings of autonomic symptoms during the follow-up. It was found that the LF, VLF, and total frequency

Table 1 Participants characteristics

		$N = 40$
First stage	Gender	
	Female	18 (45%)
	Male	22 (55%)
	Week born (wk)	31 (28–32)
	Weight (g)	1,586 (1,010–2,330)
	Apgar 5	9 (2–9)
	Apgar 10	9 (5–9)
	Days in NICU	41 (15–96)[a]
Follow-up	Age at follow-up (mo)	51 (33–66)
	Follow-up after discharge from the NICU	21 (52.5%)
	Neurodevelopmental treatment	14 (35%)
	Autonomic symptoms	11 (27.5%)
	Pain	1 (2.5%)
	Cold feet/hands	3 (7.5%)
	Constipation	3 (7.5%)
	Sleep disorder	5 (12.5)

Abbreviation: NICU, neonatal intensive care unit.
Note: Values in the table are number (%), median (minimum–maximum).
[a]$N = 30$.

Table 2 Heart rate variability measures at birth week and week 32 for 36 children according to autonomic symptom at follow-up

	HRV week born					HRV week 32				
	All $N = 36$	Autonomic symptoms at follow-up				All $N = 36$	Autonomic symptoms at follow-up			
		With $N = 9$	Without $N = 27$	*p*-Value			With $N = 9$	Without $N = 27$	*p*-Value
High frequency (msc^2)	20 (6–98)	15 (7–81)	24 (6–98)	0.33		26 (4–94)	15 (7–81)	27 (4–94)	0.565
Low frequency (msc^2)	77 (27–242)	54 (27–112)	82 (37–242)	0.024		80 (27–544)	56 (27–112)	90 (39–544)	0.005
Very low frequency (msc^2)	21 (8–71)	17 (8–22)	26 (8–71)	0.042		26 (8–87)	17 (8–22)	32 (9–87)	<0.001
Total power (msc^2)	116 (50–405)	81 (50–213)	143 (84–405)	0.017		136 (50–672)	81 (50–213)	150 (65–672)	0.012

Abbreviation: HRV, heart rate variability; msc^2, milliseconds squared.
Note: Values in the table are median (minimum–maximum); *p*-value based on Mann–Whitney U test.

Table 3 Area under the receiver operating characteristic curve and 95% confidence interval for heart rate variability indices in the week of birth and week 32 as predictors of finding autonomic symptoms at 3 to 5 years of age

		95% confidence interval	
	Area under the curve	Lower limit	Upper limit
Week born			
Low frequency (msc^2)	0.72	0.57	0.89
Very low frequency (msc^2)	0.75	0.58	0.93
Total power (msc^2)	0.76	0.58	0.95
Week 32			
Low frequency (msc^2)	0.81	0.65	0.97
Very low frequency (msc^2)	0.87	0.75	0.99
Total power (msc^2)	0.78	0.59	0.98

Abbreviation: msc^2, milliseconds squared.

indices show significantly lower values in children with autonomic symptoms during follow-up. This is true for the index of variation in birth age and those taken at week 32. For example, in the index of total power, the median value in the week of birth is lower in children with autonomic symptoms during follow-up at 62 milliseconds squared ($p = 0.017$) and at 69 milliseconds squared at week 32 ($p = 0.012$).

The area under the ROC curve was examined for each HRV index when reviewing the optimal predictor for autonomic symptoms. The area under the curve ranges from 0.72 to 0.76 at birth and from 0.78 to 0.87 at week 32. The VLF index at week 32 shows the most considerable absolute value—an area of 0.87 with a 95% confidence interval between 0.75 and 0.99 (►**Table 3**). ►**Fig. 1** shows the ROC diagram for the VLF index at week 32 as a predictor of an autonomic symptom at 3 to 5 years of age. The cutoff value that maximizes sensitivity and specificity is 20.4, with a sensitivity for detecting autonomic symptoms between the ages of 3 and 5 years of 82% and a specificity of 89%. Based on this cut point (20.4) the association between lower HRV measure at 32 GA and autonomic signs at age 3 to 5 years is 0.53 ($p < 0.001$).

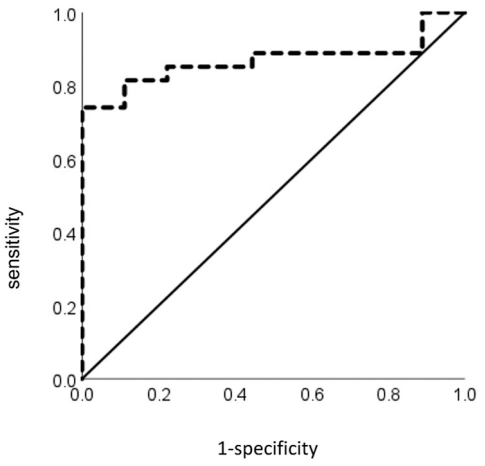

Fig. 1 Receiver operating characteristic curve for the very low-frequency index at week 32 as a predictor of having autonomic symptoms at the age of 3 to 5 years.

Discussion

The essential findings of this preliminary work are that more than 25% of the children born prematurely at 28 to 32 GA have symptoms of autonomic system dysfunction at the age of 3 to 5 years. The second important finding is that HRV indices in the week of birth and week 32 GA are significantly low among children with impaired autonomic function and can predict autonomic symptoms at ages 3 and 5.

The findings of this work that more than 25% of the children born prematurely at 28 to 32 GA have symptoms of autonomic system dysfunction at the age of 3 to 5 years join results from cross-sectional studies found impaired cardiac autonomic function in children and adults born prematurely. In these previous works, a low HRV was observed, and a longer duration for HR recovery following exertion in those born prematurely compared with those born at term age.[8,9] This work shows the prevalence of other systems impairments and other symptoms and systems impairments, thus showing the scope of the autonomic damage following premature births. The spectrum of autonomic impairments is diverse and can impact both quality of life and disease risk, particularly concerning cardiovascular diseases and mortality rates. Previous studies focused primarily on heart rhythm control damage, emphasizing associated risks.[8,9] This study delves deeper into the correlation between early-life HR control indices and autonomic system function, demonstrating that lower indices at birth are linked to greater autonomic impairment later in life. This impairment extends beyond life-threatening conditions, affecting daily quality of life through issues like pain, sleep disturbances, digestive problems, and circulation issues, all of which may foreshadow future health challenges.

The other advantage of the current work is that it is a follow-up study that can link the cardiac autonomic function in the week of birth and at 32 weeks of gestation to predict autonomic symptoms 3 to 5 years later. These autonomic impairments might be associated with an immature system at birth[12] on the one hand, being admitted in the NICU, and being exposed to multiple stimuli of noise, light, and pain on the other hand. These factors may affect ANS maturation and cause secondary autonomic impairments.[13]

In the first research step of the current work, a follow-up study was conducted from birth to 8 months corrected age. An inverse relationship was found between measures of HRV and neuromotor development.[14] In the current study, the parents were asked about treatments the child underwent in the first years of his life. Fourteen of 40 children received neurodevelopmental treatments. However, children with autonomic symptoms were not treated for their symptoms.

Despite the limitations of this work, since it is a small sample from a single medical center, and uses questionnaires only in the follow-up stage, the findings point to a common phenomenon typical of children who presented low variability indices at the week of birth/32 weeks of gestation. The information about these autonomic phenomena is less known and treated less, despite the child's daily difficulties. This issue should be further investigated.

Note

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

Ethical approval was received from the "Shaare Zedek" Hospital Ethics Committee to conduct the study and use the previous database (285-21 SZMP). All the parents signed informed consent at the NICU and agreed to participate in the follow-up study.

Authors' Contribution

Substantial contributions to conception and design: all authors; acquisition of data: N.Z. and H.I.M.; analysis and interpretation of data: M.K.L., N.Z., and H.I.M.; drafting the article: M.K.L.; revising the paper critically: all authors; final approval of the version submitted for publication: all authors.

Conflict of Interest

None declared.

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