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Genomic Insights into Congenital Heart Disease in Neonatal Cohort: University Medical Centre Ljubljana Experience

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INTRODUCTION
Congenital heart disease (CHD) is the most commonly detected congenital anomaly and affects up to 1 % of all live-born neonates. The etiology involves both genetic and environmental factors. Current guidelines support the use of Chromosomal Microarray Analysis (CMA) and Next Generation Sequencing (NGS) as diagnostic approaches to identify genetic causes. The aim of our study was to evaluate the diagnostic yield of CMA and NGS in a cohort of neonates with both isolated and syndromic CHD.

PATIENTS AND METHODS
The study included 192 neonates under 28 days of age with abnormal echocardiography findings hospitalized at the Department of Neonatology, University Medical Centre Ljubljana, between January 2014 and December 2023. Phenotypic data were obtained for each neonate by retrospective medical chart review. CMA was performed in all neonates with CHD as a first-tier genetic test. NGS was performed in neonates with normal CMA results and high clinical suspicion of monogenic disease.

RESULTS
We established the genetic diagnosis of 24 distinct syndromes in 17.2 % of cases. The most common genetic diagnoses were 22q11.2 microdeletion syndrome (15.2 %), CHARGE syndrome (12.1 %), Noonan syndrome (6.1 %), Kabuki syndrome (6.1 %), and Williams syndrome (6.1 %). In addition, we detected variants of uncertain significance in 5.2 % of cases.

CONCLUSIONS
In a cohort of 192 neonates with CHD, we were able to identify a genetic cause in 17.2 % of cases. Timely genetic diagnosis is important for the detection of syndrome-related comorbidities, prognosis, reproductive genetic risks and, when appropriate, genetic testing of other family members.
None declared

N	CHD	Extra cardiac defects	Results of genetic diagnostics	Classification	Syndrome
1	sASD	kidney anomaly	arr[hg19] 7q11.23(72,766,313-74,133,332)x1	P	Williams syndrome
2	SVAS, stenosis of both pulmonary arteries	/	arr[hg19] 7q11.23(73,474,931-73,493,893)×1	P	Williams syndrome
3	mVSD, BAV	hypotonia, hypoplasia of the corpus callosum, feeding difficulties, cryptorchidism, dysmorphic facies	46, XY, del(8)(p23.3p23.3),dup(8)(p12p23) dn	P	8p inverted duplication/deletion syndrome
4	VSD	congenital hydronephrosis, dysmorphic facies	arr[GRCh37] 10q26.13q26.3(126528827-135061104)×1	P	10q26 deletion syndrome
5	VSD, ASD	dysmorphic facies	arr[GRCh37] 22q11.21(21081260-21431174)×1	P	22q11.2 microdeletion syndrome
6	pmVSD	coloboma of irises, hypotonia, anorectal anomaly, feeding difficulty	arr[GRCh37]11q23.3q25(119369472-134904063)x1	P	Jacobsen syndrome
7	TGA, ASD, PDA	LGA	arr[GRCh37] 17q12(35149908-36214026)×3, mat	P	17q12 microduplication syndrome
			EZH2: c.2051G>A	P	Weaver syndrome
8	aortic valve stenosis, BAV, sASD	/	47, XY, +mar.ish der(22)(pter->q11.21::p12->pter)(acro-p++,SE 14/22+, CEP22+, N25+)	P	Cat eye syndrome
9	ToF, ASD	dysmorphic facies	arr[GRCh37] 1q21.1q21.2(146618988-149224043)×3 dn	P	1q21.1 microduplication syndrome
10	VSD	hypocalcemia, dysmorphic facies	arr[GRCh37] 22q11.21(18912870-21431174)×1 dn	P	22q11.2 microdeletion syndrome
11	ToF	EA/TEF	CDH7:c.5405-8C>G	P	CHARGE syndrome
12	pmVSD, multiple ASDs, PFO	SGA, palatoschisis, dysmorphic facies, proximal placement of thumb, pes calcaneovalgus	arr[GRCh37] 18q21.31q23(55111850-78002264)×1	P	18q deletion syndrome
13	VSD, ASD	renal cysts	arr[GRCh37] 17p11.2(16842163-20217777)×1	P	Smith-Magenis syndrome
14	pmVSD, truncus arteriosus,	hypothyroidism	arr[GRCh37] 22q11.21(18917796_21431174)×1,	P	22q11.2 microdeletion syndrome
15	VSD, ASD	dysmorphic facies	arr[GRCh37] 22q11.21(18917796_21431174)×1,	P	22q11.2 microdeletion syndrome

16	VSD, ASD	dysmorphic facies	arr[GRCh37] 1q21.1q21.2(146618988_147826074)×1 dn	P	1q21.1 microdeletion syndrome
17	mVSD, sASD, hypoplastic aortic arch	dysmorphic facies	arr[GRCh37] 22q11.21(18917796_21431174)×1,	P	22q11.2 microdeletion syndrome
18	ASD, PDA	dysmorphic facies	arr[GRCh37] 16p13.11(15126709_16292235)×3	P	16p13. 11 microdeletion syndrome
			arr[GRCh37] 9q34.13(134077089_134401452)×3	VUS	
19	ASD	Hypotonia, hydronephrosis	arr[GRCh37] 16p13.11(15126709_16292235)×3	P	16p13.11 microduplication syndrome
20	stenosis of aortic valve, BAV	dysmorphic features	arr(X)x1[0.8]	P	mosaic Turner syndrome
21	valvular pumonary stenosis, SVPS	dysmorphic facies, macrosomia, unilateral cryptorchidism, aplasia cutis	PTPN11:c.923A>G	P	Noonan syndrome
22	sASD	hypotonia, hypoplasia of the corpus callosum, dysmorphic features, palatoschisis, glossoschissis, hypermobility of joints, clinodactyly of 5th fingers	OFD1:c.1187_1190delTCAA	LP	Orofaciodigital syndrome I
23	AVSD	coloboma of iris, facial nerve palsy, mixed hearing loss, hypotonia dysmorphic features, feeding difficulties	CHD7:c.4353+1G>A	P	CHARGE syndrome
24	pmVSD	palatoschisis, dysmorphic features, congenital hydronephrosis, unilateral cryptorchidism, malformation of the vertebrae	KMT2D	P	Kabuki syndrome
25	sASD, BAV, PDA	dysmorphic facies, palatoschisis, widely spaced nipples, barrel chest, hypermobility of joints, clinodactyly of 5th fingers	KMT2D:c.4364dup	P	Kabuki syndrome
26	sASD, cleft mitral valve with mild MVR, PDA	dysmorphic facies, chorioretinal coloboma, vocal cord paresis, feeding difficulties, hearing loss	CHD7:c.3655C>T	P	CHARGE syndrome
27	ToF	brachycephaly, ptosis of right eyelid, coloboma of optic nerve papilla, gnatoschisis, choanal atresia, feeding difficulties, unilateral renal agenesis, dysmorphic features, hockey-stick palmar crease, partial 2-3 toe syndactyly, hypotonia, hearing loss	CHD7:c.4203-4204delTA	P	CHARGE syndrome
28			CHRNG:c.753-754del	P	

	sASD, aortic valve stenosis, BAV	AMC, dynamic upper airway obstruction, ptosis of right eyelid, cryptorchidism, bilateral congenital hip dislocation, clubfoot, fibromatosis colli	CHRNG:c.250G>A	LP	Multiple pterygium syndrome – Escobar type
29	sASD, PPS, PDA	dysmorphic facies, direct hyperbilirubinemia	JAG1:c.2122_2125del	P	Alagille syndrome
30	pulmonary valve stenosis, PDA, PFO	dysmorphic facies, LGA, renal cyst	PTPN11:c.922A	P	Noonan syndrome
31	pulmonary valve stenosis, BAV, bicuspid pulmonary valve, PFO	dysmorphic facies, bilateral coloboma of iris, macula and papilla, horseshoe kidney, ankyloglossia	CHD7:c.629C>T	P	CHARGE syndrome
32	pmVSD	hypotonia, abnormal cortical gyration, feeding difficulties, dysmorphic facies, single palmar crease	SMARCA4: c.4114C>T	LP	Coffin-Siris syndrome 4
33	left atrial isomerism	heterotaxy, polysplenia	DNAAF3:c.73_82del	LP	Ciliary dyskinesia, primary, 2

Legend: ACC – agenesia of the corpus callosum, AMC – arthrogryposis multiplex congenita, AVSD – atrioventricular septal defect, BAV – bicuspid aortic valve, CHD – congenital heart disease, CoA – coarctation of aorta, dn – de novo, DORV – double outlet right ventricle, EA/TEF – esophageal atresia/tracheoesophageal fistula, LP – likely pathogenic variant, mat – maternally inherited, MVR – mitral valve regurgitation, mVSD – muscular VSD, P – pathogenic variant, PAH – pulmonary artery hypertension, PA-VSD – pulmonary atresia with ventricular septal defect, PDA – patent ductus arteriosus, PFO – patent foramen ovale, pmVSD – perimembranous VSD, PPS – peripheral pulmonary stenosis, sASD – ASD secundum, SGA – small for gestational age, SVAS – supravalvular aortic stenosis, SVPS – supravalvular pulmonary stenosis, ToF – tetralogy of Fallot, VSD – ventricular septal defect, VUS – variant of uncertain significance

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ASSOCIATION OF PREMATURITY ON CARDIAC REMODELLING AND STRUCTURE IN CHILDHOOD

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Introduction: Advancements in intensive care has resulted in improved survival of premature babies to adulthood. Compared to adults born at term, preterm born adults have increased risk of adverse cardiovascular outcomes including hypertension and there is evidence of increase in left ventricular(LV) free wall mass, impaired LV systolic function and smaller right ventricles(RV) with increased ventricular wall mass. Disordered postnatal development of the heart could lead to this observed cardiac dysfunction later in life.
The aim of this study is to compare cardiac morphology using cardiac magnetic resonance(CMR) imaging in childhood between children born prematurely with those born at term.

Methods:Participants were ex-preterm and healthy term-born children, aged 7 to 12 years, who as neonates were recruited to studies of nutrition and body composition. Participants underwent free-breathing cine CMR with for quantification of ventricular volumes and dimensions. The primary outcome measure was LV end-diastolic volume indexed(LVEDVI) to body surface area. The secondary outcome measures were: RV-indexed end-diastolic volume(RVEDVI), ventricular stroke volumes, ventricular ejection fractions and LV-indexed myocardial mass index. Measures of ventricular function were compared between groups using independent sample t-test.

Results:33 ex-preterm children and 32 term-born children were included. The median(IQR) age of participants was 10 (9-10) years. The mean(SD) gestational age of the preterm babies at birth was 28.5 (2.2) weeks and mean(SD) birthweight was 1205 (338)g. There was no difference between the groups for the primary outcome of LVEDVI. There were also no significant differences for the secondary outcomes, other than lower indexed myocardial mass index in the preterm group compared to the term group (42.7g/m2 vs 47.4g/m2, p=0.01)

Conclusions: Other than reduced LV indexed systolic myocardial mass index in the ex-preterm group, there were no significant differences in cardiac morphology in ex-preterm children in childhood compared with their term-born counterparts. This is contrary to differences observed in preterm born adults, suggesting changes in cardiac morphology may occur in post-pubertal years. Further cohort studies are required to assess the impact of prematurity and neonatal interventions on cardiac structure in later life. These findings may suggest that targeted interventions in childhood may prevent the adverse cardiovascular outcomes observed in adulthood.
None declared

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TRACKING THE FALSE-NEGATIVE RATE: PULSE OXIMETRY SCREENING IN NEWBORNS

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Background: Congenital heart diseases (CHD) are the most common neonatal malformations, and the critical ones, which require surgical intervention or cardiac catheterization in the first year of life, represent 25%. Screening through pulse oximetry is recommended for early anomaly identification.

Methods: Conduct a one-year retrospective study to identify cases of CHD following a negative result on pulse oximetry screening in newborns with a gestational age of more than 34 weeks in a tertiary center between January 1 and December 31, 2023. Information was taken from the medical charts.

Results: A total of 2655 newborns with gestational age greater than 34 weeks underwent pulse oximetry screening between 24-48 hours of postnatal life to detect the presence of CHD. Among these, there were no positive cases identified through screening; however, one newborn with CHD was detected, despite the negative result on pulse oximetry screening. This case, at approximately 50 hours postnatal, underwent an echocardiographic evaluation as part of the screening process (the newborn presented preaxial polydactyly - bifid thumb, and deviation of the oral commissure in cries). The ultrasound assessment revealed a narrowing along the path of the aorta at the ductal insertion level and significant dilation of the suprahepatic veins. Consequently, monitoring of the newborn continued, noting pressure differences between the upper and lower limbs. Suspicion of duct-dependent malformation arose, and administration of Prostaglandin E1 was initiated. Angio-CT was performed, confirming the suspicion by identifying a total abnormal pulmonary venous return (Type III) and minimal aortic coarctation. The Cayler syndrome was discussed, but unfortunately, genetic testing hasn't been conducted. On the 8th day of life, the newborn was transferred to a specialized center for surgical intervention. The false negative rate in the analyzed batch was 0.037%, which is extremely low but has a significant impact considering the screening concept.

Conclusion: Even though there is currently a high recommendation for the use of pulse oximetry as a screening tool, in our clinic, it has not found its utility due to the presence of at least one false negative result and the absence of positive results.
Keywords: CHD, pulse oximetry screening, Cayler Syndrome

None declared

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THE EFFECT OF NOISE ON HEART RATE AND OXYGEN HEMOGLOBIN SATURATION IN NEWBORNS

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INTRODUCTION. In neonatal units, newborns are often excessively exposed to noise, which, as a stressful environmental stimulus, has numerous effects on their health, development, and treatment outcomes. The American Academy of Pediatrics (AAP) has defined permissible and critical noise levels for neonatal units, which are often exceeded. With this study, we aimed to identify noise exposure levels at the Department of Neonatology, University Children's Hospital Ljubljana and investigate whether noise affects the physiological parameters of newborns (heart rate (HR) and oxygen hemoglobin saturation (SpO2)).

MATERIAL AND METHODS. In the first part of the study the sound intensity, categorized into periods, was measured continuously with SoundEar 3-300 for 21 consecutive days. In the second part, we conducted a prospective cohort study in 30 cardiorespiratory stable newborns. With Somnomedics (pulse oximeter and ECG electrodes) we measured their HR and SpO2 concurrently with sound intensity measurements.

RESULTS. Sound intensity exceeded AAP recommended levels during the morning, afternoon, and night hours, with the morning shift being the loudest (ANOVA, $p < 0.0005$). During clinical rounds, sound intensity was higher than during feeding, care, or inactive periods (ANOVA, $p < 0.0005$). A statistically significant positive connection was observed between average noise intensity and newborns' HR (fixed effects panel regression, $p < 0.0005$), whereas statistically significant associations between average sound intensity and SpO2 were not found. 20 out of 30 newborns showed statistically significant changes in HR, 80 % of them experienced an increase in HR in response to changes in sound intensity; statistically significant changes in SpO2 were only detected in 14 out of 30 newborns, of which 71,4 % experienced a decrease in SpO2 in response to changes in sound intensity.

CONCLUSIONS. The study revealed that noise levels on the ward exceed recommended AAP values throughout the day, with the highest levels during the morning shift and clinical rounds. We demonstrated that changes in newborns' HR correlate with sound intensity, whereas this wasn't confirmed for SpO2. Our results indicate the importance of a quiet environment for maintaining the heart rate of newborns within physiological limits.

NONE DECLARED

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COMPARISON OF ULTRASOUND-MEASURED INFERIOR VENA CAVA DIAMETERS, BIOELECTRICAL IMPEDANCE MEASUREMENTS OF BODY WATER, AND BODY MASS IN NEONATES

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INTRODUCTION: Medical conditions often disrupt the physiological processes that regulate fluid balance in neonates after birth. To evaluate fluid status in neonates, daily measurements of body mass and circulation assessment are commonly used. However, these methods alone may not provide a reliable assessment. Analysis of body composition by bioelectrical impedance (BIA) and ultrasound measurement of the inferior vena cava (VCI) may provide more reliable data on fluid status in the neonate. We aimed to analyse the association between daily body mass and body water (total water (TBW) and extracellular water (ECW)) measured by BIA, and diameters and collapsibility index of the VCI measured by ultrasound.

MATERIAL AND METHODS: In a cohort prospective clinical study we included 27 neonates with different pathologies aged 1-7 days. Ultrasound measurements of VCI transversely and longitudinally during inspiration and expiration (during spontaneous breathing, 1-1.5 cm distal to the insertion of the hepatic vein), measurements of body composition by BIA and measurements of body mass were performed on each subject at least 3 times with an interval of 24-72 hours. Simultaneous measurements from the same subject were then analysed and evaluated.

RESULTS: The average proportion of TBW decreased during the first days after birth from 80.3% (day 1) to 73.1% (day 8) (GLM Repeated Measures, $p = 0.006$). The association between ECW and body mass over time was statistically significant (LEM random slope, $p < 0.001$). The association between large VCI diameter measured transversely during inspiration, body mass and ECW was statistically significant (LEM random intercept, ($p = 0.024$). No statistically significant association with ECW or body mass was found for the other ultrasound variables.

CONCLUSIONS: By measuring body composition with BIA, we confirmed the reduction in average proportions of TBW after birth and the association between body mass and ECW. Only one VCI measurement, the transversely measured large VCI diameter during inspiration, was associated with body mass and ECW. BIA may provide additional information on the fluid status of the newborn. Further research in larger numbers of subjects is needed to define the significance of VCI measurements for the assessment of fluid status in neonates.

none declared

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congenital heart disease in newborns of diabetic mothers: a prospective chohort of 120 cases

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INTRODUCTION :
Newborns of diabetic mothers (NODM) are a growing concern in the current context of obesity and diabetes mellitus pandemics. This condition can lead to significant morbidity and mortality, particularly cardiac morbidity.
The aim of this study was to screen for all types of congenital heart disease associated with diabetes during pregnancy.

MATERIAL AND METHODS :
We conducted a prospective study, from August 1, 2020 to November 30, 2020 covering all newborns of diabetic mothers, born at the maternity and neonatology center of the Farhat Hached university hospital of Sousse in Tunisia .
All newborns underwent an echocardiographic examination in the Cardiac Doppler Ultrasound laboratory.

Results:
During the study period, 120 cases of NOMD were collected. The sex ratio was 0.9.
The mean weight of newborns was 3554 g. 10% of newborns were hypertrophic. Maternal diabetes was type 1 in 2.65% of cases, type 2 in 0.88% and gestational in 96.46%. The mean age at which cardiac Doppler ultrasound was performed was 3.5 days. It was abnormal in 31.16% of cases. These anomalies were represented by hypertrophic cardiomyopathy in 10% of cases, a foramen ovale in 9.16% of cases, a persistent ductus arteriosus in 9.16% of cases, an atrial septal defect in 1.6% of cases, an interrupted aortic arch and a pulmonary stenosis in one case. Left ventricular systolic function was normal in all neonates, with a mean of 66% and extremes ranging from 59% to 76%.

Conclusion :
Cardiovascular complications in NODM represent a significant medical issue requiring increased vigilance. The potential implications for the health of these newborns underline the crucial importance of screening this population for congenital cardiac anomalies at an early stage.

None declared