Debrecen, Debrecen, Hungary, Debrecen, Hajdu-Bihar, Hungary; [5]Department of Pharmaceutical Technologies, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary, Debrecen, Hajdu-Bihar, Hungary

Background: The choroid plexus and ependyma are predominantly affected by extravasated blood upon intraventricular hemorrhage (IVH) in preterm infants causing the breakdown of the blood-brain-barrier. Hence, the impact of hemorrhage on choroid plexus epithelium is critical in potential brain damage following IVH.
Aims: We characterized the cellular, inflammatory, and oxidative responses in human choroid plexus epithelial cells (HCPEpiC) exposed to heme in vitro.
Methods: Cultured HCPEpiC were treated with heme (1–50 μM) for 1–24 hours. The NF-κB pathway activation was investigated by fluorescence microscopy, while reactive oxygen species (ROS) were measured intracellularly using CM-H2DCFDA-based assay. Expression of related signaling molecules and secreted proteins was studied by western blotting and ELISA. The blocking effects of albumin/hemopexin were also observed. To analyze the consequence of heme on global RNA expression in choroid plexus, transcriptome and miRNA pattern were investigated by RNA-sequencing and TaqMan OpenArray, respectively. ClueGO and miRTarbase databases were used for pathway and network analysis.
Results: Increased ROS production ($p < 0.001$) and induced NF-κB pathway activation without cell death was shown after treatment with 25 μM of heme. Out of 1529 significantly altered genes, 231 showed more than 2-fold upregulation and 106 were downregulated in association with the activation of inflammatory pathways (IL8, IL6, ICAM1), TLR4 signaling (IL1B) and chemical stress (HMOX1, SOD2). Significantly elevated concentrations of IL-8, IL-6, IL-1β and ICAM-1 were detected via elevated expression of HMOX1, NQO1 and SOD2 proteins in response to heme. These cellular events were prevented by albumin/hemopexin treatment. Among 355 detected miRNAs, there were 25 significantly downregulated and 10 upregulated miRNAs vs. controls. Based on the network analysis, downregulated miR-223 was associated with upregulated IL6, while reduced miR-9 and miR-505 resulted in higher SOD2 level.
Conclusion(s): Heme acts as a major mediator of the damage of choroid plexus epithelium after IVH, which contribute to neurodevelopmental impairment in preterm infants.

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Thrombosis in Neonates and Children

OC 48.4

The Throm-PED Registry: Epidemiology and Treatment of Adolescent Thrombosis

C. Van Ommen[1], L. Raffini[2], R. Bhat[3], R. Berrueco[4], M. Bordbar[5], C. Cervio[6], M. Simpson[7], N. Sirachainan[8], J. Jaffray[9], S. Saini[10], B. Branchford[11], M. Bhatt[12], R. Kumar[13], A. Barg[14], J. Blatny[15], P. Zharkov[16], R. Natesirinilkul[17], N. Montanez[18], P. Monagle[19] and L. Srivaths[20]

[1]Erasmus MC Sophia Children's Hospital, Rotterdam, Zuid-Holland, Netherlands; [2]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States; [3]Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois, United States; [4]Hospital Sant Joan de Déu, Esplugues Llobregat, Catalonia, Spain; [5]Shiraz University, Chiraz, Fars, Iran; [6]Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Buenos Aires, Buenos Aires, Argentina; [7]Rush University Medical Center, Rush Hemophilia and Thrombophilia Center, Chicago, IL, USA, Chicago, Illinois, United States; [8]Faculty of Medicine Ramathibodi hospital, Mahidol University, Bangkok, Thailand, Bangkok, Krung Thep, Thailand; [9]Rady Children's Hospital, San Diego, California, United States; [10]Department of Pediatrics, Washington University in St. Louis, St. Louis, Missouri, United States; [11]Versiti Medical Sciences Institute, Wauwatosa, Wisconsin, United States; [12]McMaster Children's Hospital, McMaster University, Hamilton, Ontario, Canada; [13]Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Harvard Medical School, Boston, Massachusetts, United States; [14]The National Hemophilia Center, and Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Ramat Gan, Israel, Tel Aviv, HaMerkaz, Israel; [15]Children's University Hospital Brno, Brno, Moravskoslezsky kraj, Czech Republic; [16]Dmitry Rogachev National Research Center, Moscou, Moskva, Russia; [17]Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, Chiang Mai, Chiang Mai, Thailand; [18]University of Texas Health Science Center of Houston, McGovern Medical School, Gulf States Hemophilia and Thrombophilia Center, Houston, Texas, Houston, Texas, United States; [19]Haematology Research, Murdoch Children's Research Institute, Melbourne, Victoria, Australia; [20]University of Texas Health Science Center of Houston, McGovern Medical School, Gulf States Hemophilia and Thrombophilia Center, Houston, Texas, United States

Background: Pediatric venous thromboembolism (VTE) has a bimodal age distribution with peaks noted in infancy and adolescent years. Few studies have investigated the epidemiology and specific management of VTE in adolescents.
Aims: To evaluate the epidemiology and management of VTE in adolescents in comparison to younger children.
Methods: The Throm-PED registry is an international, multicenter, prospective disease registry of the International Pediatric Thrombosis Network (IPTN). In the basic VTE registry the following data are prospectively collected: age at diagnosis, gender, VTE type, location, risk factors and treatment. Categorical variables were compared using the chi-square or Fisher exact test, as applicable, using SPSS software.
Results: Since inception of the registry in 2019, 1191 children (≤18 years; n = 608 male) with VTE have been included. The median age at VTE diagnosis was 5 years, 420 patients (35%) were ≥12 years old (adolescent cohort). More female patients were present in the adolescent cohort compared to the younger cohort (Table 1). In the adolescent cohort, VTE was more frequently located in the lung and upper extremity, and less frequently in the brain, jugular vein and inferior vena cava than in the younger cohort. VTE risk factors that were more often present in adolescents included immobility, oral contraception, COVID-19 infection, obesity and congenital thrombophilia, whereas central venous catheters, non COVID-19 infection and congenital heart disease were less common. Most adolescents received antithrombotic treatment. Direct oral anticoagulants, vitamin K antagonists and thrombolysis were more often administered to adolescents than younger children.

Table 1 Epidemiology and management of venous thromboembolism in adolescents compared to younger patients

	< 12 years (n=771)	≥12 years (n=420)	OR (95% CI)	P-value
Age (mean)	2.6 years	15.1 years		
Female	346 (45%)	229 (55%)	1.5 (1.2-1.9)	<0.001
Location				
Lower extremity	218 (28%)	132 (31%)	1.2 (0.9-1.5)	NS
Lung	20 (3%)	96 (23%)	11.1 (6.7-18.3)	<0.001
Upper extremity	126 (16%)	91 (22%)	1.4 (1.1-1.9)	0.023
Intracranial	129 (17%)	43 (10%)	0.6 (0.4-0.8)	0.002
Jugular vein	96 (12%)	36 (9%)	0.7 (0.4-0.99)	0.042
Subclavian vein	39 (5%)	17 (4%)	0.8 (0.4-1.4)	NS
Inferior vena cava	52 (7%)	13 (3%)	0.4 (0.2-0.8)	0.008
Heart	44 (6%)	11 (3%)	0.4 (0.2-0.9)	0.015
Superior vena cava	19 (2%)	10 (2%)	1.0 (0.5-2.1)	NS
Renal vein	20 (3%)	3 (1%)	0.3 (0.1-0.9)	0.026
Risk factor				
Central venous line	457 (59%)	104 (25%)	0.2 (0.2-0.3)	<0.001
Malignancy	52 (7%)	84 (20%)	1.2 (0.8-1.7)	NS
Immobility	79 (10%)	75 (18%)	1.9 (1.4-2.7)	< 0.001
Infection	211 (27%)	75 (18%)	0.6 (0.4-0.8)	< 0.01
COVID-19	16 (2%)	25 (6%)	3.0 (1.6-5.7)	< 0.001
Oral contraception*	0 (0%)	57 (25%)	1.3 (1.2-1.4)	< 0.001
Surgery	138 (18%)	57 (14%)	0.7 (0.5-1.1)	NS
Cong. heart disease	146 (19%)	13 (3%)	0.1 (0.1-0.2)	< 0.001
Obesity	9 (1%)	53 (13%)	12.2 (6.0-25)	< 0.001
Cong. thrombophilia	17 (2%)	35 (8%)	4.0 (2.2-7.3)	< 0.001
Previous VTE	49 (6%)	28 (7%)	1.1 (0.7-1.7)	NS
Treatment				
LMWH	598 (78%)	306 (73%)	0.8 (0.6-1.1)	NS
UFH	156 (20%)	97 (23%)	1.2 (0.9-1.6)	NS
DOAC	56 (7%)	148 (35%)	6.9 (5.0-9.7)	<0.001
VKA	31 (4%)	42 (10%)	2.7 (1.6-4.3)	< 0.001
Thrombolysis	16 (2%)	25 (6%)	3.0 (1.6-5.7)	< 0.001
No treatment	81 (11%)	11 (3%)	0.2 (0.1-0.4)	< 0.001

Abbreviations NS not significant, Cong congenital, VKA vitamin K antagonists, DOAC direct oral anticoagulants, LMWH Low molecular weight heparin, UFH unfractionated heparin, OR odds ratio, CI confidence interval; *only in female patients

Conclusion(s): Epidemiology and treatment were different in adolescents compared to younger children. More detailed evaluation of adolescent thrombosis will help to develop tailored preventive and management strategies in this age group.

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OC 67.5

Clinical Outcomes of Neonatal Catheter-Related Thrombosis: A Multicenter Retrospective Cohort Study

M. Pelland-Marcotte[1], M. Desjardins[2], N. Singbo[3], A. Hébert[4], A. Lapointe[5], C. Sabapathy[6], A. Zabeida[7], K. Kumar[7], S. Tole[8], M. Bhatt[9], M. Liebman[2], J. Déry[10], J. Wong[11], A. Amid[11] and M. Beltempo[6]

[1]Centre Hospitalier Universitaire de Quebec, Universite Laval, Quebec City, Quebec, Canada; [2]Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; [3]Recherche Clinique et Évaluative - Centre de recherche du CHU de Québec, Quebec City, Quebec, Canada; [4]Centre Hospitalier Universitaire de Québec, Quebec City, Quebec, Canada; [5]Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada; [6]Montreal University Health Center, Montreal, Quebec, Canada; [7]The Hospital for Sick Children, Toronto, Ontario, Canada; [8]Children's Hospital - London Sciences Health Center, London, Ontario, Canada; [9]McMaster Children's Hospital, McMaster University, Hamilton, Ontario, Canada; [10]Faculté de Médecine, Université Laval, Quebec City, Quebec, Canada; [11]British Columbia Children's Hospital, Vancouver, British Columbia, Canada

Background: Neonates are at high risk of thromboembolism (TE), especially neonates requiring central venous catheters (CVC). Management of neonatal TE is particularly complex, as the higher risk of bleeding must be balanced with thrombotic risks.

Aims: Describe treatment modalities and clinical outcomes among neonates with CVC-related TE.

Methods: A retrospective cohort study enrolled neonates ≤28 days of life requiring a CVC for ≥24 hours with a radiologically confirmed TE in the anatomical territory of the CVC, admitted in one of seven Canadian NICUs (2013–2018). Data from the Canadian Neonatal Network registry were linked to clinical outcomes of interest in individual medical records, namely TE resolution and TE progression within three months, major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) defined using ISTH criteria. Logistic regression explored predictors of anticoagulation use and whether treatment modality predicted clinical outcomes. Institutional review boards of all sites approved the study.

Results: Overall, 377 neonates (median gestational age: 34.3 weeks, range: 22–41) sustained a TE, diagnosed at a median of 12 days (25–75th percentile: 5–26) after birth (Table 1). Expectative management with or without CVC removal, anticoagulation and other treatment strategies (thrombolysis or antiplatelets) were used in 218 (58%), 149 (40%) and 10 (3%) patients, respectively. Older gestational age, male sex, occlusive TE, and TE location were independently associated with anticoagulation use (Table 2). Complete TE resolution and progression occurred in 42.9% and 2.5% of patients, while MB and CRNMB happened in 7.7% and 4.1% of neonates. Clinical outcomes did not significantly differ based on treatment modality (TE resolution: p = 0.941, TE progression: p = 0.202, MB: p = 0.531, CRNMB: p = 0.052).

Table 1. Patient characteristics

	N (%) (n=377)
Male sex	210 (55.7)
Gestational age at birth	
<28 weeks	118 (31.3)
28^{+0} – 31^{+6} weeks	46 (12.2)
32^{+0} – 35^{+6} weeks	66 (17.5)
≥36 weeks	147 (39.0)
Concomitant medical diagnoses	
Respiratory distress syndrome	186 (49.3)
Necrotizing enterocolitis	59 (15.6)
Culture-proven clinical sepsis	29 (7.7)
Underlying central venous catheter type[a]	
Umbilical vein catheter	297 (78.8)
Peripherally inserted central catheter	183 (48.5)
Jugular or femoral vein	44 (11.7)
Other (including Broviac)	13 (3.4)
Thrombosis location	
Upper or lower limb	101 (26.8)
Umbilical/portal vein	170 (45.1)
Intra-cardiac and pulmonary	11 (2.9)
Other (including vena cava, multiple sites)	95 (25.2)
Occlusive thrombus on imaging	123 (32.6)
Presence of accompanying symptoms	
Clinical symptoms	134 (35.5)
Thrombocytopenia without other symptoms	52 (13.8)
Asymptomatic (including line dysfunction alone)	191 (50.7)
Initial diagnostic method	
Doppler Ultrasound	320 (84.9)
Echocardiography	52 (13.8)
Computed tomography	2 (0.5)
Magnetic resonance imaging	3 (0.8)

[a] Patients could have ≥1 catheter. All patients had at least one central venous catheter.