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Diabetology, endocrinology

Genetic causes of extreme tall stature in children

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Introduction: The aetiology of tall stature (TS) is heterogeneous. After excluding an endocrine disorder, the specific cause of TS frequently remains unsolved and tall children are therefore given only a descriptive diagnosis of familial tall stature (FTS)or idiopathic tall stature (ITS). Only a small percentage of tall children are genetically examined.

Aim: To elucidate genetic cause of excessive growth of children with extreme TS (ETS) using next-generation sequencing (NGS) methods.

Results: Altogether we identified a genetic cause of ETS in 5/33 (15%) children. One child had Supermale syndrome (karyotype 47, XYY), 1 Sotos syndrome (variant c.5374_5375insGA in *NSD1* gene), 1 Simpson-Golabi – Behmel syndrome (variant c.81delinsTTC in *GPC3* gene), 1 had likely pathogenic variant in *PPP2R5D* gene (c.1422G>A) and 1 had likely pathogenic variant in *SUZ12* gene (c.1627delT). Moreover, in additional 5/33 (15%) children we found variants of uncertain significance in genes *COL1A1, PTCH1, COL6A2, TET3, FGFR3.*

Conclusion: Genetic findings typically associated with syndromic tall stature could also be found in extremely tall children without classical clinical features associated with the specific syndromic disease.

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Thyroid disturbances after SARS-CoV-2 infection in children

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Background: Rapidly evolving clinical data have raised awareness of the possible connection between the novel coronavirus (SARS-CoV-2) and thyroid disturbances. Reactivation of previous, and new onset autoimmune thyroid disorders after coronavirus disease 2019 (COVID-19) suggest a potential effect of the virus in triggering or accelerating autoimmunity. However, studies among the pediatric population are still in its infancy.

Aims: Our aim was to assess the prevalence, characteristics and permanency of thyroid disorders diagnosed after SARS-CoV-2 infection in children.

Methods: Data were collected in a prospective registry of a pediatric Long COVID outpatient clinic at Semmelweis University, Budapest (Dept. of Paediatrics, Bókay Unit). We collected the following parameters from all children regardless of their symptoms: sex, date of birth, history of previous thyroid disease, thyroid laboratory values (anti-thyroid peroxidase [ATPO], antithyroglobulin [ATG], thyroid-stimulating hormone [TSH], and free thyroxine [fT4] if the TSH was altered). In cases of any abnormal thyroid value, thyroid ultrasound was performed, necessity of medication was determined and follow-up visits were carried out.

Results: From 24th March, 2021 to 23rd March, 2022, 303 children with confirmed previous SARS-CoV-2 infection were enrolled in our study. Mean±SD age was 12.3±3.8 years, and 136 (44.9%) were male. From further analysis we excluded three patients with a preexisting thyroid disorder. Thyroid autoimmunity was found in 19 children (6.3%), TSH was altered in five of them (three increased and two decreased). Isolated TSH abnormality (all elevated) was seen in an additional four children (1.3%). Of the nine children with alterations in TSH, only one girl had elevated fT4 (her TSH was below 0,002 mU/L), the others had normal fT4 values. After the first visit, we initiated hormone replacement therapy in two cases and anti-thyroid treatment in the above-mentioned girl with elevated fT4. Of the 23 children with any thyroid alteration, initial ultrasound was performed in 22 cases and among those, 12 showed signs of thyroiditis. Of the 23 children with a newly found thyroid alteration, 22 were followed for a mean (±SD) of 13.0 (±4.8) months. Seventeen long-lasting and five transient disturbances were seen. During the follow-up period, two children developed thyroiditis and one girl had to start hormone replacement therapy.

Conclusions: We found a remarkable amount (7.6%) of previously not diagnosed thyroid disturbances after COVID-19. To assess if these alterations can be connected to SARS-CoV-2, further, controlled studies are needed. To determine if these disturbances persist, we initiated long-term follow-up of our children.

Funding: The study was supported by the ÚNKP-22-3-I new national excellence program of the Ministry of Culture and Innovation from the source of the National Research, Development and Innovation Fund. Sponsors had no role in the design, data collection, analysis and interpretation of the results.

Thyroid hormones and food preferences in children and adolescents with obesity

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Keywords: food preference, children, obesity, thyroid hormones

Background and Aims. Thyroid hormones affect energy metabolism. However, their interrelation with food preference, which might contribute to childhood obesity development, are much less understood. Here we investigated if changes of thyroid hormone levels are paralleled by specific modulation of food preference and potentially linked to the level of obesity in children and adolescents.

Patients and Methods. Interrelations between food preference and peripheral thyroid activity were examined in a population of 99 non-obese and 101 obese children and adolescents (12.8±3.6 yrs. of age, 112/89 F/M) randomly selected from the patients of Obesity and Metabolic Disease Out-patient Research unit at NÚDCH in Bratislava in a period between 12/2017 and 3/2020.

Results. Obese children and adolescents had lower preference for the food rich in high sucrose, and high-complex carbohydrates, while the preference for protein and fat containing food and that for dietary fibers was identical in obese and non-obese. In obese adolescents positive correlations of FT4 with the preference for high protein, high fat rich diet was found irrespective of the fatty acid unsaturation level. Moreover, FT4 correlated negatively the preference for dietary fibers which was also exclusively found in obese adolescents. Obese individuals with higher FT4 levels (stratified by median value) had higher systemic levels of AST and ALT then the low FT4 group. Multiple regression analysis with age, sex, BMI-SDS and FT4 as co-variates revealed, that FT4 and gender are the major predictors of variability in the preference for diet high in protein, fat and monounsaturated fatty acids. FT4 was the sole predictor of the preference for diet containing saturated and polyunsaturated fatty acids as well as for diet low in fibers.

Conclusions. Serum levels of thyroid hormone FT4 were significantly associated with food preferences in obese children and adolescents. This may indicate that FT4 could contribute to development of childhood obesity and its complications by modulating food preference.

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Cross sectional study of iodine statut among children following plant-based diet compared to omnivores in the Czech Republic

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Background: Vegetarian (VG) and vegan (VN) diets are getting more and more popular even in paediatric population. Excluding animal sources in nutrition may impar physiological development and growth. Other problem may be a lack of up-to-date epidemiological studies. Iodine is an essential micronutrient that play a major role in physiological thyroid function, and especially vegan diet may be insufficient in it.

Aims: To describe an iodine status and iodine intake in a group of children following plant-based diet e.g., vegan or vegetarian.

Methods: In our study, we gathered clinical, anthropometric, and blood/urine data on iodine status and thyroid function from children aged 5.4 (±4.3) years who followed either a VG diet (n = 91), VN diet (n = 75), or omnivore diet (OM, n = 52).

Results: In our study, we discovered that there were no significant variations in the levels of thyroid-stimulating hormone (TSH), triiodothyronine (fT3), thyroglobulin (TG), or Anti-thyroid Peroxidase Antibody (ATPOc) among the VG, VN, and OM groups. However, we observed that fT4 levels were unexpectedly higher in the VN group compared to the OM group (15.00±1.73 vs. 16.17±1.82 pmol/L, $p<0.001$). Additionally, the presence of anti-thyroglobulin antibodies (AhTGc) was notably more common in the VG (17.4 %)/VN (17.9 %) groups than in the OM group (3.8%) ($p<0.001$). We measured the lowest (5.99 µg/L) and highest (991.80 µg/L) levels of AhTGc in the VN group. Among the VN and VG children, 31 each were found to have iodine deficiency based on the criteria of UIC < 100 µg/L. Those who received regular iodine supplementation had higher UIC levels ($p<0.001$). The vegan group exhibited a lower mean daily intake of iodine (MDI). A significant percentage of the VG (83.7 %, n = 77) and VN (78.2 %, n = 61) groups did not take any supplements.

Conclusions: The higher prevalence of iodine deficiency was observed in plant-based group; with possible impact on thyroidal health. Further research – cohort studies – is needed and new guidelines for iodine supplement use in the particular group is also warranted.

Funding: The study was supported by the project LX22NPO5104, Funded by the European Union – Next Generation EU, and by Charles University program COOPERATIO METD and COOPERATIO PEDI and Ministry of Health, Czech Rep., no. NU21-09-00362

Parameters of glycemic control by treatment and monitoring modality in children with type 1 diabetes: Population-based study

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Background: Recently introduced hybrid closed loop technologies (HCL) represent a promising option for the improvement of glycemic control. Several randomized control trials or real-life data showed their safety and effectiveness. However, data comparing all treatment and monitoring modalities on a population level are still scarce.

Aims: To assess the association of the key parameters of glycemic control with treatment and monitoring modalities including hybrid closed-loop algorithms in children with T1D (CwD) using the data from the national pediatric diabetes registry ČENDA.

Methods: CwD younger than 19 years with T1D duration >1 year were divided according to the treatment modality and type of CGM used: multiple daily injections (MDI), insulin pump without (CSII) and with HCL function, intermittently scanned continuous glucose monitoring (isCGM), real-time CGM (rtCGM) and intermittent or no CGM (CGM-). HbA1c, times in glycemic ranges and glycemia risk index (GRI) were compared between the groups.

Conclusions: CwD treated with HCL achieve better glycemic control in comparison with children using other treatment modalities. HCL technology should be considered as a modality of choice for all children fulfilling the indication criteria

Vitamin D and parathormone in children with hypertension, obesity and mild chronic kidney disease

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Background: There is overwhelming evidence of vitamin D (vitD) importance in health including cardiovascular prevention. A level of 75 nmol/L is recommended, however, the benefits of achieving these levels are less evident in pediatric research, especially in children with obesity, hypertension, and chronic kidney disease (CKD). VitD and parathormone (PTH) form a tightly controlled feedback cycle, PTH being a major stimulator of vitD synthesis in the kidney while vitD exerts negative feedback on PTH secretion. Both hormones have direct effects on the endothelium, heart, and other vascular structures. Considering the increasing prevalence of childhood obesity and hypertension, research on cardioprotective role of vitD is an important approach.

Aims: The purpose of this study was to find potential differences in vitD and PTH serum levels between three groups: normal-weight children with hypertension, overweight children with hypertension and children with mild CKD.

Methods: The study included 133 children and adolescents between 5 and 19 years old. 30 had hypertension (group A), 37 were overweight with hypertension (group B), 43 had mild CKD (group C), and 23 were healthy (group D – control group). Anthropometric and blood pressure (BP) measurements were performed and vitD, PTH and other laboratory parameters, potentially influencing the cardiovascular health, evaluated: glucose, uric acid, creatinine, sodium, potassium, chloride, calcium, magnesium, phosphate, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides (TG), cystatin C, apolipoprotein A1 (apo A), apolipoprotein B (apo B), homocysteine and alkaline phosphatase (ALP).

Results: The results showed statistically significant differences in PTH serum levels in all groups, A and D ($p < 0.001$), B and D ($p < 0.001$), C and D ($p = 0.002$), as well as in body mass index (BMI), systolic BP, glucose, uric acid, creatinine, creatinine clearance, ALP, sodium, chloride, phosphate, TG, HDL cholesterol, LDL cholesterol, apolipoprotein B and vitD. Although no significant differences were observed in serum vitD levels comparing individual groups to the control group, in all groups vitD levels were below 75 nmol/L.

There were statistically significant correlations between vitD and BMI, diastolic BP, uric acid, creatinine clearance and homocysteine as well as between iPTH and ALP, systolic and diastolic BP, creatinine, calcium, cystatin C and homocysteine.

Conclusions: We conclude that children with hypertension, obesity and mild CKD all have lower values of vitD. Our findings indicate there is need to redefine the currently accepted cut off values for vitD supplementation for different groups of children at risk, necessitating further research.

Neonatology, intensive therapy in pediatrics

Synchronous cerebral rSO_2 and mean arterial pressure changes in neonates undergoing general anaesthesia

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Introduction, aims, hypothesis: Hemodynamic instability is a critical event and a common finding during neonatal general anaesthesia. Addition of NIRS (near-infrared spectroscopy) to the standard monitoring may help preventing adverse events. NIRS provides real time information about regional cerebral tissue oxygenation (rSO_2), which is mainly influenced by blood pressure (BP), peripheral oxygen saturation (SpO_2), heart rate, and partial CO_2 tension (pCO_2).

We aimed to assess the episodes of low cerebral oxygenation and its relation to low BP in a tertiary neonatal surgical centre.

Methods: In this observational prospective study between June 2021 to November 2022, we enrolled 67 infants (38 premature and 29 term neonates) undergoing general anaesthesia. The rSO_2 was registered using NIRS monitor. Decreased rSO_2 levels were defined as <70% rSO_2. For hypotension for <7 days old preterm infants mean arterial pressure (MAP) was defined less than their gestational age in weeks, in infants >7 days old MAP was adjusted to recommendations by J. de Graaff [1]. Data is in median [IQR] or number (%).

Results: Median bodyweight of premature patients was 2.1 [1.4;3.2] kg and term neonates were 3.3 [2.8;3.8] kg. A total of 6824 mins were recorded. Episodes of decreased rSO_2 occurred median 2 [1;4] times and lasted for 42.5 [7.8;79] mins in preterm and 21 [0;55] mins in term neonates. RSO_2 decrease were recorded in 49% of time in premature; and 32% in term neonates. The total time spent in low rSO_2 range was longer in preterm than in term neonates ($p<0.001$). In premature infants, synchronous MAP and rSO_2 decrease was observed in 28% of the total time. In contrast, we observed these rates in term neonates in 13% and 20%, respectively. Spearman's correlation coefficient indicated significant correlation between MAP and rSO_2 values in preterm infants ($r=0.28$, $p<0.001$). Additionally, there was no correlation between MAP and rSO_2 values in term neonates.

Discussion: Our data shows that rSO2 decrease is frequent during neonatal anaesthesia, suggesting that it is prudent to use NIRS monitoring in this patient population. Interestingly, in term neonates 'isolated' hypotension without rSO2 change occurred 20% of the time, a finding of high clinical relevance that warrants further investigation.

[1] de Graaff JC, Pasma W, van Buuren S, et al. Reference Values for Noninvasive Blood Pressure in Children during Anesthesia: A Multicentered Retrospective Observational Cohort Study. *Anesthesiology* 2016; **125**: 904-13

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End-tidal carbon dioxide monitoring in neonates receiving therapeutic hypothermia for hypoxic-ischemic encephalopathy

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Background: The consistently described association between hypocapnia and adverse outcomes in infants with hypoxic-ischemic encephalopathy (HIE) suggest that continuous carbon-dioxide (CO_2) monitoring is an important technique and its use should be encouraged. End tidal ($etCO_2$) monitoring enables the prevention of undesired partial pressures of CO_2 (PCO2) by facilitating immediate intervention. The primary aim was to evaluate the agreement between $etCO_2$ and temperature corrected PCO_2 values in patients with HIE receiving hypothermia (TH).

Methods: In this prospective observational single center trial, infants receiving TH for HIE at the Department of Pediatrics, Semmelweis University between 2020 December to 2021 October were enrolled. Neonates during TH are mechanically ventilated as per local protocol. The level of $etCO_2$ was monitored via Capnostream 35 portable respiratory monitor (Medtronic, Dublin, Ireland) using sidestream end tidal capnography with 20/s sampling rate. The mean $etCO_2$ was determined over 10 min periods preceding the time of the blood gas. Arterial, capillary blood samples were collected as part of routine care, based on the decisions of the attending physicians. The agreement between $etCO_2$ and temperature corrected PCO_2 was analyzed by using the Bland Altman plot.

Results: Twenty-six mechanically ventilated infants with HIE were assigned to the trial, and were monitored for $etCO_2$ for a median 70 hours [IQR 63; 78], starting from a median 11. [7 ; 23] hours of life, corresponding to hypothermia and rewarming. A total of 315 paired $etCO_2$ and temperature corrected PCO_2 measurements were analyzed including 130 arterial and 185 capillary samples. The $etCO_2$ was closely related to the arterial PCO_2 with the average difference of -2.5 mmHg (limit of agreement -13.9; 8.9 mmHg), whereas for capillary samples the average difference was -8.8 mmHg (limit of agreement -23.6; 6.0 mmHg). Hypocapnia was frequent based on continuous etCO2 measurements, neonates spent a median 31% [IQR 13; 46] of time below the target $etCO_2$ range of 35-55 mmHg. Hypercapnia (> 55 mmHg) was rare, occurring in less than 1% of time.

Conclusion: The routine use of continuous $etCO_2$ monitoring has the potential to improve the intensive care of newborns with HIE by avoiding the extreme levels of CO_2 and may optimize long-term neurological outcomes.

The effect of retinal hemorrhage on the treatment of retinopathy of prematurity

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Background: Specific diseases of preterm infants have a huge effect on their quality of life. ROP (Retinopathy of Prematurity) is the leading cause of childhood blindness besides visual cortical impairment and optic nerve hypoplasy. The key of the pathomechanism is the fact that the retinal vascularization of a preterm child is incomplete. Oxigenisation changes between the mother's womb and after delivery, which leads to an abnormal neovascularization of the developing vessels through VEGF (vascular endothelial growth factor). Laser therapy is used to destroy the VEGF-producing cells of the retina. The other main treatment option is antibody-based therapy, which blocks the VEGF protein itself.

Aims: Our aim was to determine whether the retinal haemorrhage observed during ROP is an innocent phenomenon in terms of VEGF formation or can be evaluated as a new risk factor.

Methods: Both clinical and laboratory methods were used. We did a retrospective analysis of ROP cases from the past 10 years and determined the incidence of ROP associated with gestational weeks. Based on the presence or absence of retinal haemorrhage, we divided patients into two groups and assessed the rate of laser treatment. In our *in vitro* model, we measured the expression of VEGF of the ARPE (retinal epithelial) cells influenced by heme. Gene and protein level studies were also performed (qPCR, ELISA).

Results: Data from more than 1000 VLBW (very low birth weight) preterm infants suggest that the prevalence of different stages of ROP in our Clinic is in line with international data. As a national centre for neonatal central nervous system surgery, we had the opportunity to collect 460 cases of ROP. Compared to the group without retinal haemorrhage, we found a significantly higher rate of laser treatment in cases with the presence of bleeding. Our *in vitro* studies demonstrated that in the presence of heme, ARPE cells have shown significantly elevated VEGF expression in both gene and protein levels in a dose- and time-dependent manner.

Conclusions: Our results suggest that heme is not an innocent phenomenon in the progression of ROP. Through excessive VEGF production, it enhances pathological neovascularization so we should evaluate the presence of retinal bleeding as a new risk factor.

Circulating microRNAs in plasma of infants with neonatal sepsis: A preliminary study

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Background: Neonatal sepsis still to this day poses a major problem in neonatal care. Incidence and mortality are staggeringly high, as four in ten infants with sepsis die or experience a major disability resulting from sepsis. In the context of inflammatory diseases, previous studies identified microRNAs (miRNAs) as potential new targets of therapeutical interest. Studies show that miRNAs are involved in inflammatory processes, which leads us to hypothesise that dysregulation of miRNA expression could contribute to developing neonatal sepsis. Moreover, dysregulation of specific miRNAs could be facilitated as an early biomarker of sepsis development and/or clinical outcome in newborns.

Material and methods: We collected a cohort of 98 patients with newborn sepsis and 22 control patients without signs of systemic infection. Specimens of peripheral blood were collected and processed. One part of the specimen was frozen as whole blood, and the rest was processed to yield the blood plasma. In the septic group, peripheral blood was collected on day one after the onset of symptoms and again on day three and day seven, when available. In the control group, only one peripheral blood specimen was collected on the day of admission. We chose 64 septic patients and all 22 collected controls for our profiling study. Total RNA enriched for small RNA has been extracted from blood plasma. Based on a literature search, we decided to measure levels of circulating miRNAs (hsa-miR-29a-3p, hsa-miR-96-5p, hsa-miR-185-5p, hsa-miR-16-5p, hsa-miR-15a-5p, hsa-miR-132-3p, hsa-miR-223-3p, hsa-miR-26a-5p) using quantitative polymerase chain reaction. The results have been normalized to the average expression of all measured miRNAs and analysed using GraphPad Prism 8 statistical software.

Results: We successfully validated several miRNAs that have been shown to be dysregulated in patients with neonatal sepsis. Moreover, we have shown that there is some potential in miRNAs as disease development-monitoring endpoints.

Conclusion: To our knowledge, this is the first study targeted at an independent evaluation of existing results. We successfully validated some of the previous observations and provided novel information regarding disease monitoring using miRNAs. Our results provide necessary preliminary data for further research and the development of medical care for patients with neonatal sepsis.

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Usage of continuous propofol infusion at the pediatric intensive care unit

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Background: Propofol related infusion syndrome (PRIS) is a high mortality condition in children that occurs after high doses and long duration of propofol infusion. Incidence is unknown, but estimated to be less than 0.4%. Since it is a serious complication, guidelines suggest a maximum dose of 4 mg/kg/hour for less than 48 hours to be used in pediatric patients.

Aims: The main goal of this study is to survey the usage of propofol at the Pediatric Intensive Care Unit (PICU), and to investigate whether there is any detectable difference between patients who received propofol infusions and those who did not.

Methods: In our retrospective study, we included 34 admissions, the ages varied from 1 month to 17 years. The group of propofol infusion recipients consisted of 22 admissions.

Results: The cumulative doses of propofol infusions varied between 6 and 702.14 mg/kg, with the average of 112.47 mg/kg (SD 149.24 mg/kg). The average of peak doses was 3.46 mg/kg/hour, with the maximum of 10 and the minimum of 0.97 mg/kg/hour (SD: 1.83 mg/kg/hour). The average duration of propofol infusion was 39.5 hours (SD: 63.32 hours), the longest being 297, the shortest being 2 hours. Since there were significant differences in age ($t(33.85)=3.8$, $p = .001$) and disease severity scores ($t(33.05)=2.75$, $p = .01$) between the groups, we included those as covariates in our regression models. Mortality was not associated with propofol infusion (OR=0.02, 95% CI [0 4.22] p=.34). Propofol had no effect on PICU length of stay (OR = 0.02, 95% CI [0 11.4] p = .25). Propofol was not associated to the need for fluid resuscitation (OR=0.38, 95% CI [0.07 1.94], p=.24) or the administration of vasopressors (OR=1.63, 95% CI [0.2 19.36], p=0.658). Heart rate ($t(21)=-1.03$, p=.313, MD= 4.72, 95% CI [-14.24 4.79]) and mean arterial pressure ($t(21)=-0.08$, p=.938, MD=-0.23, 95% CI [-6.18 5.72]) did not show significant changes 6 hours after the propofol infusion had started. There were no significant differences between groups in the studied laboratory parameters.

Conclusions: In conclusion we did not find any significant difference between patients who did and who did not receive continuous propofol infusion, and we did not discover any case of PRIS or severe complication due to propofol infusion.

Rare diseases - new challenges in CF and SMA

Magnetic resonance imaging of the lung in children with cystic fibrosis

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Background: Cystic fibrosis (CF) is a chronic progressive multiorgan disease severely affecting the respiratory health in children. The severity of the respiratory disease is the main determinant of the morbidity and mortality; therefore, the respiratory system should be monitored from early childhood. Besides the lung function tests, lung imaging is an important part of the follow-up assessments. Despite the adverse effect of the frequent radiation on the children's health, chest X-ray and computed tomography (CT) are still the gold-standards for lung imaging. Due to the technical development of the magnetic resononance imaging (MRI), MRI can be employed in the assessment of the lungs.

Aims: Our aim was to establish an MRI protocol that is suitable in children and able to detect the CF-related lung disease in a wide range of severity.

Methods: A team of radiologists, pediatric pulmonologists, MRI physicists and technicians was established. Healthy volunteers and children with CF with good cooperation were recruited from the Pediatric Department (Semmelweis University). Multiple sequences, including functional imaging of perfusion were selected based on the literature and optimized for the study population. The MR images then were analyzed by a radiologist who was blind to the clinical data of the children. Two MRI scoring systems were selected from the literature and combined to fit the most to our MRI protocol. Mucus plugs, bronchodilation, bronchial wall-thickening, atelectatic and dystelectatic segments, consolidations, pleural effusions, and perfusion were included in the scores. As a validation of the MRI scoring, the relationship between the scores and lung function data (forced expiratory volume in the 1st second of expiration, FEV1) from the same day was assessed.

Results: Over the assessment of healthy volunteers, the duration of the test decreased from 90 to 35 min. The final MR protocol contained 7 sequences, including the measurement of perfusion. MRI was successful in all participants. In CF patients (age: 14+/- 2,4years, BMI: 15,7+/-1,5kg/m2), FEV1 ranged between 27,5 and 102% reflecting mild to severe lung disease. The lower the FEV1 was, the more extended was the lung damage on the MRI images, which reflected in the higher MRI scores (r=0,896, p=0.006). The score of perfusions showed the strongest relationship with FEV1 (r=0,94, p<0,001).

Conclusions: Our MRI protocol was suitable in children and reflected the severity of the lung disease. MRI can be a promising tool in monitoring the respiratory disease in children with CF without exposure to radiation.

Feasibility of lung function testing in infants involved in the newborn cystic fibrosis screening

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Background: Cystic fibrosis (CF) is the most common autosomal recessive inherited disease in the Caucasian population, causing severe respiratory impairment. Due to its prevalence, high morbidity and novel therapies, CF has become a focus of research in recent decades. Although several attempts have been made to improve respiratory function testing, there is still no technique available to assess respiratory function in children from infancy throughout childhood, especially outside of a research setting, in a busy outpatient clinic.

Aims: Our aim was to employ a novel lung function method, the oscillometry as a part of the recently established newborn screening for CF. We aimed to assess the feasibility of the test in a routine clinical setting.

Methods: The newborn screening for CF commenced in January 2022 in Hungary. From the initial blood test, children who were at high risk of CF were identified. The selected children were invited for a sweat test to either of the two screening centers in Hungary. Children who came for the sweat test at the Department of Pediatrics (Semmelweis University) were approached and following a written consent by the parents, lung function test was attempted during sleep. Oscillometry was recorded during spontaneous breathing via a facemask for 5 minutes. Respiratory impedance was measured between 7 and 47 Hz and respiratory resistance and compliance were calculated.

Results: Between July and December 2022 sweat tests were not available due to the lack of one essiential component of the test Europe-wide. Over this period, genetical analysis was performed in all children without the possibility of a lung function testing. From the 75 children who arrived for sweat test, oscillometry was attempted in 32 infants (14 boys) whose age varied between 5 weeks and 4 months. In 6 cases quiet sleep was not achieved, 3 babies did not have a stable breathing pattern and in two measurements technical error occurred. Successful lung function measurements were performed in 21 infants (success rate: 66%). Resistance and compliance were on average 31,78 hPa.s/L and 0,068 mL/hPa, respectively.

Conclusions: Our results suggest that oscillometry is suitable for infant testing even in a busy clinical outpatient setting. The success rate of the test can be improved with development of an appropriate environment that is more suitable for sleeping. The clinical use of the test in the monitoring of lung function in infants and older children with CF needs further confirmation.

A stitch in time saves nine – abnormal glucose tolerance in patients with cystic fibrosis: Systematic review and meta-analysis

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Background: Basic science results suggest that abnormalities of the endocrine pancreas in cystic fibrosis (CF) occur earlier than hitherto estimated. All stages of the abnormal glucose tolerance (AGT) spectrum are associated with declining pulmonary function and increased mortality which could be reduced by early recognition and treatment. Despite, screening for AGT is recommended only from 10 yoa according to the current guidelines.

Research design and Methods: We registered our systematic review and meta-analysis protocol via PROSPERO (CRD42021282516). Literature search was conducted in MEDLINE (via PubMed), Embase and Cochrane Register of Controlled Trials (CENTRAL) for studies reporting data about the prevalence of AGT or its subtypes in CF populations. General and superselected populations (e.g.: pancreas exocrine insufficient, ΔF508 homozygous) were separately analyzed. Pooled proportions, risk and odds ratios with 95% confidence intervals (CI) were calculated in at least three age subgroups (pediatric, adult, mixed/unknown). One-stage dose-response random effect meta-analysis was used to assess the effect of age on CF- related diabetes (CFRD).

Results: 457 studies and data from 520 544 patients were involved in the quantitative analysis. More than one third of the patients are affected by AGT in childhood (0.31 [95% CI 0.25-0.37]), even under the age of 10 0.33 [95% CI 0.23-0.44], and half of the adults have AGT (0.51 [95% CI 0.45-0.57]). The prevalence of prediabetes remains unchanged (impaired glucose tolerance in chwCF: 0.14 [95% CI 0.10-0.18]) vs. awCF: 0.19 [95% CI 0.14-0.25]), while the proportion of CFRD increases by age (<5 yoa: 0.005 [95% CI 0.0001-0.15]; 5-10 yoa: 0.05 [95% CI 0.01-0.27]; 10-18 yoa: 0.11 [95% CI 0.08-0.14]; >18 yoa: 0.27 [95% CI 0.24-0.30]).

Conclusion: Accurate knowledge of the global prevalence of AGT and its subtypes is essential to develop a better screening strategy. Reconsideration of the current guidelines and better awareness are needed for screening and treating AGT in CF, especially under 10 yoa, to delay the disease progression and maintain a better life quality.

First experiences of newborn SMA-screening in Hungary

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Introduction: Developing a disease-modifying medication was a revolutionary leap forward regarding the treatment of congenital Spinal Musclar Athrophy (SMA). The initiation of disease modifying treatment has a great impact on quality of life, however, in symptomatic patients only particular limited results could be achieved using disease-modifying treatment. Therefore the early (presymptomatic) diagnosis and treatment is critical in SMA neonates.

Newborn screening for SMA was implemented to ensure early diagnosis in symptom-free infants; more than 90% of USA newborns and more than 45% of European newborns were tested by the end 2022.

Since 1975, Hungarian healthcare system has provided a compulsory screening for 28 diseases complying with the Wilson-Junger criteria. Since November 2022, newborn SMA screening has begun in Hungary as part of an international research programme.

The aim of this presentation is to demonstrate our first experiences in SMA screening as well as the disease modifying treatment administered to a symptomless SMA-I. newborn.

Method: An expert committee was set up, who has developed the research program and initiated the launch of the SMA screening, led by Semmelweis University and the University of Szeged, Hungary. Bethesda Children's Hospital has a coordination role in this research program. After the evaluation and approval of the submitted research program, the pilot study of National Newborn Screening Program began on November 1, 2022 setting up the screening method and verifying its reliability. SMA screening is state-funded, voluntary on the part of both parents and healthcare institutions, and requires a specific informed consent of participation. The test is performed from a blood sample (DBS, Dried Blood Spot) during the first days of life. The method is a two-step DNA-based PCR test specially developed for newborn screening of SMA. At first, DNA is isolated from DBS, followed by a QPCR test for homozygous deletion of the SMN1 gene.

Results: In the first 2 months, 54.9% of newborns were screened for SMA, with negative results. In the second 2 months, the number of newborns receiving SMA screening increased to 69.8%. In January 2023, the first positive screening result was obtained in a 5-day-old, asymptomatic newborn, whose SMA type was confirmed by molecular genetic testing 3 days later. The clinical geneticist immediately referred the family to an SMA treatment center, where the newborn received gene replacement therapy at the age of 22 days without any complication. She was the youngest SMA patient who received therapy in Hungary so far. There was no false-positive results during the first 5 months of screening.

Summary: Newborn SMA-screening is a well supported agenda in Hungarian society. Our experiences support that initiation of treatment as early as possible decreases the patient's, their families and also society's burdens. Patients diagnosed with SMA have a reasonable chance to achieve quality of life comparable to their healthy peers. Continued success of this international program will hopefully complete the Hungarian mandatory newborn screening program with SMA screening as well.

Associations between age at initiation of therapy and achievable quality of life in patients receiving gene replacement therapy

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Backround: Gene replacement therapy has revolutionized the management of spinal muscular atrophy (SMA). At the Bethesda Children's Hospital (Budapest, Hungary), 27 children underwent gene therapy between October 2019 and February 2023. The study aims to explore the correlation between age of onset and treatment outcomes.

Patients and method: The criteria for gene replacement therapy were homozygous deletion of the SMN1 gene with up to 3 SMN2 copies, NIV support for a maximum of 16 hours per day, low anti-adenovirus antibody titers, physiological organ functions, no infections, and an 8-week gap between the last nusinersen dose and gene therapy. After eligibility assessment, patients received onasemnogene abeparvovec in an isolated ward, followed by immunosuppressive medication and ulcer prophylaxis. Weekly check-ups were conducted for a month to assess the immune response, followed by complex assessments at 3 months and periodic follow-up exams at regular intervals.

Results: The study included data from 25 children who had at least 3 months of follow-up. All had homozygous deletion of the SMN1 gene, with 19 having 2 SMN2 copies and 6 having 3 copies. Before treatment, 37% required tube feeding, and 78% needed NIV. Eighty percent had prior nusinersen therapy, resulting in CHOP INTEND score improvement and reduced NIV dependence. Gene therapy was given at an average age of 1.49 years.

After follow-up at an average age of 3.1 years, children who did not require NIV or instrument feeding before gene therapy remained technology-independent. Three children stopped NIV completely, and six were limited to night-time hours only. CHOP INTEND increased from a mean score of 29.3 to 48.5, and HFMSE increased by an average of 13.8 points. Gene therapy effectiveness had an inverse correlation with age.

Conclusion: The study underscores the significant benefits of gene therapy in reducing technology dependence and enhancing motor development in SMA patients. However, the study also highlights the need for early (presymptomatic) screening to reduce the time lag between birth and diagnosis

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Translational medicine and basic science

The role of RNA immunity in childhood obesity

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Childhood obesity is a serious public health crisis and a critical factor that determines future obesity prevalence. Signals affecting adipocyte development in the early postnatal life have a strong potential to trigger childhood obesity, however these signals are still poorly understood. We have shown recently that mitochondrial RNA (mtRNA) efflux stimulates the transcription of nuclear-encoded genes for mitobiogenesis and thermogenesis in adipocytes of young mice and human infants (*Nat. Metab*. 2022, 4, 1684–1696). Albeit cytosolic mtRNA is a potential trigger of interferon-response, young adipocytes are lacking such response to cytosolic mtRNA, due to the suppression of interferon regulatory factor 7 (IRF7) expression in young adipocytes. We also show that breast milk-derived non-coding RNA species similarly trigger a thermogenic program in young adipocytes. Sensing cytosolic RNA species hence appears to function as a retrograde mitochondria-to-nucleus signaling and a mother-to-child mediators. This is a novel metabolic role of RNA immunity in adipocytes, that evokes thermogenic potential during early adipocyte development and protects against obesity.

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Microplate-based in vitro assays to investigate the main functions of fibroblasts

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Background: Fibroblasts play a central role in fibroproliferative diseases associated with excessive deposition of extracellular matrix (ECM). Investigation of different properties of fibroblasts, including their migration, proliferation and ECM production is unavoidable both in basic research and in preclinical drug development.

Aims: In the present study we aimed to summarise microplate-based *in vitro* assays developed or optimized by our research group to examine the main fibroblast functions.

Methods: We established a new Transient Agarose Spot (TAS) assay to investigate cell migration. This method is based on the transitional exclusion of the cells by agarose droplets, placed in the middle of cell-culture plate wells. The dynamic of gap closure, detected by microscopy and graphical analysis indicates the migration capacity of the examined cells. The fibroblast proliferation can be determined by a colorimetric assay using thiazolyl blue tetrazolium bromide dye (MTT), staining viable cells attached to the bottom of cell culture plate. The extent of cell death can be estimated based on the lactate dehydrogenase (LDH) enzyme activity of the cell supernatant. ECM production of fibroblasts can be determined by SiriusRed. Currently we are working on a complex method where the de novo synthetized, immature and mature collagens can be quantified parallelly.

Results, conclusion: During the last few years we optimized several methods to investigate the migration, proliferation and ECM production of fibroblasts. These functional assays are useful tools to reveal the unknown effect of various cytokines (basic research), to screen the efficacy of antifibrotic drug candidates (drug development) or to examine therapeutic success on individual cell cultures (translational research).

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Characterization of adipose tissue macrophages in a metabolically healthy pediatric population

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Background: Adipose tissue inflammation is a key factor leading to obesity-associated diseases since adipose tissue-derived inflammatory mediators impede insulin sensitivity, may cause beta cell destruction, and may also exacerbate autoimmunity. Adipose tissue macrophages (ATMs) are one of the key immune cells that initiate adipose tissue inflammation. ATM number is strongly increased in the obese adipose tissue, concomitant with a pro-inflammatory activation. However, ATMs are present at birth and are necessary for early adipocyte development.

Aims: ATMs may be prevalent in the adipose tissue during infancy and childhood, which are life periods critical for adipose tissue expansion and remodeling. The functions of ATMs however remain unknown in this setting. Our aim is to characterize the ATM population in metabolically healthy adipose tissue in infancy and childhood.

Methods: Adipose tissue specimens were collected during elective surgery, and anthropometric data of the donors were recorded. We specified BMI values of the respective donors. Macrophages were labeled with immunohistochemistry and also analyzed with fluorescence-activated cell sorting (FACS). Phagocytosis assay was used to define the amount of mature ATMs in the adipose tissue.

Results and conclusions: ATMs were prevalent in the adipose tissue depots in both genders and of all ages studied, and the amount of ATMs appeared to be unrelated to BMI. FACS analysis confirmed the existence of a resident ATM population in the adipose tissue of infants and children, that was relatively consistent in size during postnatal development. Preliminary observations on mouse ATMs suggested the presence of an IL-6 expressing ATM pool after birth. Given the role of IL-6 in early adipocyte commitment to the thermogenic differentiation program, it is plausible that human ATMs play an equivalent role during postnatal development of the adipose tissue. In summary, ATMs are constitutively present in the adipose tissue of infants and children.

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Fluvoxamine ameliorates TGF-β2-induced fibrotic changes in trabecular meshwork cells

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Background: Trabecular meshwork (TM) is the main pathway of aqueous humor drainage. Fibrotic-like remodeling of the actin cytoskeleton in TM cells results in extracellular matrix protein accumulation, increased stiffness and impaired outflow. These are the primary causes of increased intraocular pressure, which is the main risk factor of glaucoma, however, the exact pathomechanism is not known. The level of transforming growth factor-β2 (TGF-β2), a main driver of eye fibrosis, is increased in the aqueous humor of glaucoma patients. Sigma-1 receptor (S1R) was shown to be protective in the retina, however, its role in the TM region is unknown. Recently, we proved that the specific S1R agonist fluvoxamine (FLU) is antifibrotic in the kidney.

Aims: Here we investigated the effects of FLU on the TGF-β2-induced fibrotic response in cultured human trabecular meshwork (HTM) cells and mice anterior segment (AS).

Methods: Fibrosis of the AS was induced in C57BL/6J mice by intracameral TGF-β2 injection. AS were collected and F-actin was visualized with Phalloidin and detected with confocal microscopy. The effect of FLU on TGF-β2-induced cell proliferation, cytoskeletal rearrangement, and fibrosis-related protein levels was investigated by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay, Phalloidin staining and Western blotting respectively.

Results: F-actin enhancement was observed upon TGF-β2 injection *in vivo,* indicating fibrotic-like changes. *In vitro,* TGF-β2 induced cytoskeletal rearrangement with increased F-actin- bundles and clumps formation ($p<0.001$) that were reduced by FLU ($p<0.001$). Furthermore, FLU also inhibited cell proliferation ($p<0.05$) in TGF-β2-treated cells. The profibrotic protein levels of connective tissue growth factor, fibronectin, collagen type IV, and alpha-smooth muscle actin were all elevated by TGF-β2 treatment ($p<0.001$), while the S1R agonist prevented the elevation of these fibrosis elements ($p<0.01$; $p<0.001$). TGF-β2 also reduced the expression of Matrix Metalloproteinas-2 ($p<0.05$), which was inhibited when TGF-β2 was combined with FLU ($p<0.05$).

Conclusions: FLU may reduce the fibrotic response of trabecular meshwork and could be a potential candidate for the treatment of fibrosis-induced ocular hypertension.

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The cellular and molecular pathomechanism of peritoneal dialysis associated-fibrosis: PARK7 as a potential diagnostic and therapeutic target

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Background: Peritoneal dialysis (PD) is an effective kidney replacement therapy of end-stage renal disease in children and adults as well. After a certain period of time, the inflammatory and fibrotic processes of the peritoneal membrane induced by repeated infections and the treatment itself lead to reduced PD efficiency. PARK7 is a multifunctional protein proved to have significant antioxidant and anti-inflammatory properties in multiple diseases.

Aims: The aim of our project was to determine the presence of PARK7 in the peritoneum and its role in the pathological processes leading to peritoneal fibrosis.

Methods: The presence of PARK7 was investigated in peritoneal dialysis effluents (PDE), peritoneal tissue samples of PD-treated pediatric patients and mice, in human primary peritoneal fibroblasts (pFB) and human peritoneal mesothelial cells (HPMC). To examine mesothelial-mesenchymal (MMT) transition of PDE-treated HPMCs, the mRNA expression of tight-junction molecules was determined. The level of cellular oxidative stress in endothelial cells (HUVEC) after PDE treatment was determined by the redox-sensitive DCFDA dye. Proliferation of pFBs was measured by MTT assay after induction with PDGF-B. In our in vivo experiment, we induced peritoneal fibrosis in mice by multiple intraperitoneal injections of chlorhexidine digluconate (CG). To investigate the effect of PARK7 in our in vitro and in vivo experiments CAS-724737-74-0, a PARK7-binding compound was used.

Results: PARK7 was present in the PDE, peritoneal tissue samples and in the primary cells. Treatment of cells with PARK7-binding compound inhibited the MMT of HPMCs, reduced the oxidative stress of HUVECs and the proliferation of pFBs. Moreover, PARK7 activation resulted in beneficial effect on peritoneal fibrosis in the CG-treated mice, since it reduced the scar tissue accumulation in the submesothelial layer.

Conclusions: Our results showed that PARK7 may play a significant protective role in the pathological processes of the peritoneum leading to tissue fibrosis. We demonstrated that pharmaceutical activation of PARK7 has an antifibrotic effect in vitro and in vivo, as well.

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Role of peritoneal dialysis derived extracellular vesicles in the mechanism of fibrosis

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Introduction: Peritoneal scarring is a common complication of peritoneal dialysis (PD), characterised by the activation of mesothelial cells (MC) and fibroblasts (FB). Extracellular vesicles (EVs) are nanoparticles surrounded by a double lipid bilayer, whose main role is to provide intercellular communication.

Aim: We investigated the effect of PD effluent (PDE)-derived EVs (PDE-EV) on the activation of primary MCs and FBs.

Methods: EVs were isolated by ultrafiltration and size exclusion chromatography from the PDE of children receiving PD. The effects of PDE-EVs on the proliferation and collagen production of peritoneum-derived MCs (P-MC) and FBs (P-FB) and PDE-derived FBs (PDE-FB) were investigated by MTT, Sirius Red assays or real-time polymerase chain reaction.

Results: PDE-derived EV reduced the endogenous- and PDE-induced proliferation and collagen production of all three investigated cell types. EV treatment increased the expression of TGF-βR1 and PDGF-RA and -RB of P-MCs compared to control cells. In the case of PDE-FBs, expression of TGF-βR1 and PDGF-RB increased upon EV treatment compared to control, however, EV treatment reduced PDE-induced TGF-βR1 expression to control levels, but further increased the expression of PDGF-RA and -RB. EV treatment decreased the expression of TGF-βR1-3 and PDGF-RA and –RB of P-FBs. EV treatment increased the PDE induced TGF-βR3 expression of P-FBs compared to PDE treated P-FBs.

Conclusion: PDE-EVs significantly affect the PDE-induced proliferation and collagen production of MCs and FBs *in vitro,* Although PDE-EV treatment affected the expression of TGF-β and PDGF-B receptors in the examined cells, their changes did not explain the effect of PDE-EVs on the activation of the investigated cells. Therefore, further studies are needed to elucidate the exact mechanism of PDE-EV-s on the activation of MCs and FBs.

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Animal model of mucosal inflammation (gastritis) and its application in balneology

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Introduction: Inflammatory diseases of the mucous membrane located in various organs of our body, such as the gastrointestinal tract or respiratory system, are common diseases of children and adults. Since the end of the 17th century, the positive effects of natural mineral water Vincentka from Luhačovice Spa (Czech Republic) on inflamatory diseases have been empirically known.

The aim of this pilot study is to verify on an animal model of gastritis - as an example of mucosal inflammation - empirically reported improvement in health during drinking therapy of Vincentka natural mineral water.

Methods: Sixteen Wistar laboratory rats (one-month-old males, weight 240-280 g) used in the experiment were divided into two groups. Control group of animals (Co) received standard water at a daily dose of 0.9 ml/100 g of their current body weight through an orogastric tube for the first 7 days, and the other group of animals (Vi) received the same dose of Vincentka instead of water. Before starting the application of liquids, an adaptation phase (handling) took place in all animals for 1 week. On the eighth day, gastric inflammation was induced in both groups of animals using indomethacin solution at a dose 1 ml/100 g. Twenty-four hours after the administration of indomethacin, the experiment was terminated. Blood was collected by intracardiac puncture, accompanied by dissection and removal of the stomach and duodenum. The collected tissues and blood were further examined by an immunohistochemical and biochemical methods. The experiment was approved by Ministry of Education, Youth and Sports MSMT-35703/2019-2.

Results: We found significantly higher values of the parameters of the antioxidant capacity of the blood plasma in the Vi versus Co group: concentration of the sulfanyl group 225.5 (219.9-272.0) vs. 184.6 (108.4-234.8 μmol/L), $p<0.05$; 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid 0.104 (0.105-0.815) vs. 0.103 (0.102-0.104 (mgGA/ml)), $p<0.05$. Histological microscopy showed a reduced number of peptic erosions and ulcerations of the stomach in group Vi ($p<0.01$).

Conclusion: We can assume that "Vincentka mineral water from a natural healing source" is probably the cause protecting the GIT mucosa from the effect of acute inflammation, increases the antioxidant capacity of the body and also reduces signs of oxidative stress.

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Nephrology, nephrogenetics

Do nephrotic syndrome sera from children induce different transcriptomic profiles in human podocytes cultured *in vitro*?

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Background: Primary nephrotic syndrome affects children of any age. The uniform initial six-week-long high-dose glucocorticoid treatment is still used nowadays despite the fact that 20 % of patients do not respond at all and every patient is at risk of serious side effects, such as repeated and severe course of infections due to immunodeficiency, blurred vision due to cataract, obesity, growth failure and osteoporosis. Besides neonatal period and infancy where genetic cause and thus glucocorticoid-resistance is very probable, reliable prognostic markers of treatment response, which could be applied before commencing glucocorticoid therapy, are still missing.

Aims: Our aim was to reveal whether human immortalized podocytes cultivated with sera from children with steroid-sensitive and steroid-resistant nephrotic syndrome would induce different gene expression profiles.

Methods: We collected sera from nine children immediately upon disease manifestation, before glucocorticoids were indicated, who were later diagnosed as steroid-sensitive nephrotic syndrome. Five additional sera were obtained from children with known idiopathic steroid-resistant nephrotic syndrome with long-term disease remission and at least six months after cyclosporine discontinuation. Fully differentiated human immortalized podocytes were cultivated with 10 % patient sera for three days. After cultivation, the podocytes were lysed, RNA was isolated and 3'-mRNA libraries were prepared and sequenced. Differential gene expression and gene set analysis were performed.

Results: Steroid-sensitive and steroid-resistant nephrotic syndrome sera indeed induced distinct transcriptomic profiles of the podocytes. A total of 116 genes were significantly differentially expressed between cells exposed to steroid-sensitive vs. resistant nephrotic syndrome sera. Eighty-six genes were down-regulated and 30 were up-regulated. Gene set analysis identified 41 differentially regulated pathways between steroid-sensitive vs. steroid-resistant nephrotic syndrome sera. The upregulated pathways (35/41) represented redox reactions, DNA repair mechanism, mitosis, protein synthesis and cytoskeleton remodeling. The rest of the pathways were downregulated and were associated with cholesterol biosynthesis.

Conclusions: Our analysis showed that nephrotic syndrome sera probably contain a factor that induce significantly different transcriptome profiles of human podocytes *in vitro* with regard to later response of the child to initial glucocorticoid therapy. Experiment on larger cohort is needed to confirm the link between subject serum-induced transcriptomic profile of podocytes and clinical response of the subject to glucocorticoid treatment and further disease development. Based on the results, molecular mechanism of the disease may be elucidated and potentially lead to more efficient and targeted treatment of patients with nephrotic syndrome.

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Cellular basis of the dominant inheritance in *NPHS2*-associated glomerulopathy

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Background: The most common cause for autosomal recessive podocytopathies are mutations in *NPHS2*. The encoded podocin, a key component of the slit diaphragm, oligomerizes via two C-terminal oligomerization sites. Recently, we showed that podocin decreases the distance between neighboring nephrin molecules, ultimately reducing the size of the glomerular pore. Two families with autosomal dominant focal segmental glomerulosclerosis (FSGS) were found to carry *de novo* heterozygous *NPHS2* mutations in the last exon, affecting the second oligomerization site of podocin (p.L330Pfs*17 [c.989_992delTGTC] and p.L330Vfs*15 [c.988_989delCT]).

Aim: We aimed to determine the effect of wild-type (wt) podocin on the nephrin-nephrin distance in the presence of the *de novo* podocin mutants.

Methods: Two nephrin constructs tagged with Förster Resonance Energy Transfer (FRET) pairs were transiently coexpressed with haemagglutinin-tagged (HA) and V5-tagged podocin variant(s) in HEK293 cells. FRET efficiency between the two nephrin constructs was measured by time-correlated single photon counting in living cells 48 hours after incubation.

Results: The dominant and the wt podocin variants strongly colocalized. In accordance with our former results, the wt podocin increased the FRET efficiency, i.e. reduced the distance between the nephrin constructs. This effect was abolished when any of the two dominant NPHS2 variants was coexpressed with wt podocin (V5-wt+HA-wt vs V5-wt+HA-L330Pfs*17: $p=4.1x10^{-4}$, V5-wt+HA-wt vs V5-wt+HA-L330Vfs*15: $p=4.0x10^{-4}$).

Conclusions: Wild-type podocin is unable to reduce the distance between nephrin molecules in the presence of any of the two de novo podocin variants, suggesting an altered heterooligomerization. It explains the dominant negative effect of these podocin mutants and thus the observed exceptional dominant transmission of *NPHS2*-associated glomerulopathy.

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The overlapping patterns in clinical presentation and heterogeneity of clinical outcome in genetically distinct polycystic kidney disease patients

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Background: Polycystic kidney disease (PKD) is a large heterogeneous group of inherited conditions with a risk of end stage kidney disease (ESKD) during life. The genetic background is a key predictor of either kidney decline in adulthood or during childhood. However, a subset of patients present with unusual phenotypes and only genetic analysis can reliably distinguish them.

Aims and methods: The aim of the study was to evaluate the clinical picture of patients with PKD and analyze the atypical course of those who were genetically diagnosed with a different molecular disease as initially expected.

Results: Autosomal dominant PKD (ADPKD) was genetically confirmed in 136 patients, among them 50 children. *PKD1* and *PKD2* gene mutation was found in 113 and 23 cases, respectively. Clinical picture corresponded with the molecular result. Autosomal recessive PKD (ARPKD) was genetically confirmed in 27 children, 63% had prenatal or perinatal manifestation, 70% had arterial hypertension, 89% displayed USG signs of liver fibrosis and the mortality rate was 26%. Nephronophthisis was correctly supposed in 3 patients with *NPHP1* gene mutations in 1 and *TMEM67* gene mutations in 2 patients, respectively. Another 6 patients were clinically diagnosed with ARPKD, however genetic result confirmed ADPKD in 3, nephronophthisis type 3 in 1, *HNF1B*-associated disease in 1 and a combination of nephronophthisis type 4 and *HNF1B*-associated disease in 1 patient. *NPHP3*- and *NPHP4/HNF1B*-associated phenotypes were lethal for the patients in infancy. Two ADPKD patients had clinical courses very similar to ARPKD patients with early onset hypertension and large kidneys. The last 2 patients (ADPKD and *HNF1B*-associated disease) got stabilized after infancy with mild course of kidney disease.

Two patients clinically resembled to have nephronophthisis, one girl with ESKD within the first year of life and one boy with prenatally enlarged kidneys and postnatal kidney size asymmetry with small cysts. Genetic analysis confirmed *HNF1B*-associated nephropathy in both.

Conclusions: Despite the growing knowledge of PKD subtypes, the phenotypic overlap between them often does not allow to make a definite diagnosis according to clinical picture. Genetic diagnostics enables us to recognize precise molecular etiology of the disease. This might be important for the genetic counseling of the family as well as prognosis and further management of a child with some form of PKD.

Peritoneal mesothelial and endothelial cell barrier and its modifications in chronic kidney disease and peritoneal dialysis – from molecules to function

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Background: Solute transport across cell barriers follows paracellular and transcellular routes. In the peritoneum knowledge on the underlying molecular structures, their cell specific expression, regulation and function in chronic kidney disease (CKD) and in peritoneal dialysis (PD) is scant.

Methods: RNA sequencing and gene enrichment analysis was applied to polarized primary (HPMC) and immortalized human peritoneal mesothelial (MeT-5A), microvascular (HCMEC) and umbilical vein endothelial (HUVEC) cells followed by western blotting (WB), confocal and single molecule localization microscopy (SMLM). Arteriolar transcriptome and proteome datasets of non-CKD, CKD5 and PD children (n=6/group) underwent targeted transport pathways analysis. Key transporter proteins were quantified in parietal peritoneum (n=20-30/group) and related to peritoneal transport rates. Barrier function was studied *in vitro* (transepithelial electrical resistance, TER, and molecular weight dependent flux), *ex vivo* and *in vivo*.

Results: Junction, transmembrane and transcytotic transporter gene expression and protein abundance was highly cell type specific. Claudin (CLDN)1 is the predominant mesothelial, CLDN-5 the endothelial sealing claudin. TER reflecting functional junction status, was 50% lower in HCMEC compared to the other cell lines. Creatinine, 4- and 10-kDa dextran permeability was higher. At nanoscale, SMLM revealed lower spatial organisation of CLDN-5 in HCMEC.

In sheep peritoneum, removal of the mesothelium abolished tissue TER. In mice, short-term LPS exposure to modify mesothelial permeability resulted in faster transperitoneal 4- and 70-kDa dextran transport, suggesting a specific barrier function of the mesothelium.
In humans, peritoneal endothelial surface area per section was age dependently 1.5- to 2-fold higher than the respective mesothelial surface area. Tight junction proteins CLDN-1 to -5, and -15, ZO-1, occludin and tricellulin, and transcellular transporter ENaC, PIT1, and SGLT1 were present in mesothelial and arteriolar endothelial cells. In CKD mesothelial CLDN-1 and arteriolar CLDN-2 and -3 were more abundant than in non-CKD controls, and PD patients had highest mesothelial and arteriolar CLDN-1 and mesothelial CLDN-2, lower mesothelial and arteriolar CLDN-3 and lower arteriolar ENaC. Peritoneal creatinine/glucose transport correlated with arteriolar CLDN-2 and with mesothelial CLDN-4 and -15, which are pore forming junctions, and for creatinine with mesothelial PIT-1, a sodium/phosphate co-transporter.

Conclusion: We provide the first in-depth analysis of cell specific peritoneal determinants of solute transport and evidence for significant barrier function of the mesothelial monolayer. In humans,

peritoneal junction and transporter protein expression is modified by CKD and PD and pore forming junction proteins associate with dialytic small solute transport. These represent promising targets for therapeutic intervention.

Ultrasound elastography of liver and kidney in paediatric patients with hypertension or chronic kidney disease

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Background: Ultrasound elastography is an ultrasound technique used to assess the elasticity of tissues, providing information about tissue mechanical properties unlike any other imaging technique. It is an increasingly used researched method of measuring tissue elasticity properties in various fields in the pediatric population.

Aims: The aim of our study was to assess feasibility of ultrasound elastography in children and young adults with hypertension or chronic kidney disease (CKD) in relation to anthropometric measurements, laboratory studies and other functional or imaging studies applied in cardiovascular health. Additionally, ultrasound elastography results were interpreted according to obesity status.

Methods: 46 patients with CKD stage 1 or 2 (Group 1), 50 patients with hypertension (Group 2) and 33 healthy children, adolescents and young adults to provide a control group were included. In all, anthropometric, laboratory and some functional studies indicating increased cardiovascular risk along with liver and kidney elastography were performed.

Results: In both groups, liver elastography parameters were increased compared to the control group: Group 1 vs. control group with $p=0.007$ for speed module and $p=0.006$ for pressure module, and Group 2 vs. control group with $p<0.001$ for both modules. In kidney elastography, the only difference was for the speed module in Group 1 compared to the control group ($p=0.049$). Kidney elastography parameters were significantly higher in Group 2 when compared to Group 1. Additionally, all participants were divided according to overweight/obesity and normal-weight status, where both liver and kidney parameters were significantly higher in group of overweight/obese subjects (with p values of <0.001 in liver and left kidney, and $p=0.002$ and $p=0.001$ in right kidney for speed and pressure module, respectively). Kidney function parameters, such as creatinine and cystatin C, did not correlate with kidney elastography parameters.

Conclusions: Ultrasound elastography of liver and kidney is feasible in pediatric patients with either mild CKD or hypertension showing increased liver stiffness parameters in both groups, further aggravated by obesity. In obese CKD patients kidney stiffness also increased indicating a negative effect of clustering cardiovascular risk factors leading to decreased kidney elasticity. Liver ultrasound elastography is helpful in assessing hepatic steatosis, while kidney ultrasound elastography is less informative, at least in patients with only mild CKD. Anyway, in the latter group with some additional cardiovascular risk its role may be important. Further research on ultrasound elastography is warranted.

Urinary tract infections are associated with NETosis in children

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Introduction: Urinary tract infections (UTI) represent one of the most common bacterial infections in children. UTI are mainly in infants and toddlers associated with frequent hospital admissions. UTI treatment is aimed to prevent recurrencies and renal scarring that might be connected to complications including hypertension, proteinuria, and progression to chronic kidney disease in adulthood. The diagnosis of UTI is based on clinical picture, laboratory examination of inflammatory activity, urine sediment examination and urine culture that can occur independently of each other. Extracellular DNA (ecDNA) is released from dying cells during apoptosis, necrosis or from activated immune cells in a process of neutrophil extracellular traps (NETs) formation – called NETosis. Beside antimicrobial function activated neutrophils might have pro-inflammatory effect and thus contribute to renal damage. The aim of our study was to describe the role of NETosis in pediatric patients with UTI.

Methods: In the study were included 98 children (an average age of 1.1 years) who met diagnostic criteria (CRP≥50 mg/l, ≥ 50 000 colonies of *E. coli* per mL of catheterized urine, leukocyturia). Fifty-one healthy children with an average age of 3.6 years were enrolled in the control group. Concentrations of ecDNA were assessed using fluorescent method (Qubit dsDNA HS Assay Kit, Invitrogen, Carlsbad, CA, USA). Subcellular origin of DNA was determined using quantitative PCR method. Concentrations of cathelicidin and myeloperoxidase (MPO) were assessed using commercial ELISA kits (Human Myeloperoxidase DuoSet Elisa Kit, R&D Systems, Minneapolis, USA; LL-37 Human Elisa kit, Hycult Biotech, Wayne, PA, USA).

Results: Albeit no significant differences between groups in plasma ecDNA, children with UTI had 4-times higher levels of urinary ecDNA than healthy children ($p \leq 0.001$). Correspondingly, ncDNA and mtDNA were 3-times higher in children UTI than in controls ($p \leq 0.05$). Similarly, concentrations of urinary cathelicidin and MPO were significantly higher in UTI patients in comparison to healthy controls ($p \leq 0.001$). Concentrations of cathelicidin and MPO mutually positively correlated with ecDNA in urine ($r=0.56$, $p \leq 0.001$; $r=0.53$, $p \leq 0.001$) and leukocyturia ($r=0.27$, $p \leq 0.05$; $r=0.29$, $p \leq 0.05$).

Conclusions: Increased concentrations of markers of NETosis ecDNA, cathelicidin and MPO indicate activation and subsequent NETosis of neutrophils in urinary tract. It is well-known that individual components of NETs might stimulate activation of other immune cells, and thus contribute to "vicious circle". We hypothesize that the removal of ecDNA and NETs, which aggravate neutrophil activation and NETosis, may contribute to reducing inflammation.

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Infectology, COVID-19, epidemiology

Long COVID syndrome in children: the dysfunction of neutrophilic granulocytes as a possible pathological explanation

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Background: COVID-19 disease is an upper airway infection caused by the SARS-CoV-2 virus. Long COVID syndrome (LCS) is one of its complications, when the symptoms of the illness persist, or new symptoms occur after 4 or more weeks of the infection. Even children, whose acute illness is mostly mild, suffer from long COVID syndrome in about 10-25% of all cases. The symptoms of the disease are diverse and fluctuating, usually more organ systems are affected, and the quality of life is impaired. The need for aimed diagnosis and therapy is vital, still, the pathophysiology is not clear yet.

Aims: We purposed to discover the possible pathological role of neutrophilic granulocytes in long COVID syndrome, by examining the phagocyte functions and the cytokine environment of the cells.

Methods: Between April 2021 and April 2023 we examined 27 children suffering from LCS (LCS Group) and 24 children without LCS symptoms (Control Group). We compared the data of the clinical details, acute COVID-19 infection, long COVID symptoms, and quality of life and functioning of the two groups. We isolated serum and neutrophilic granulocytes (PMN) from the peripheral blood of the children and examined the superoxide production and the phagocytosing capacity of the PMNs, as well as the IFN-γ, IL-8, and IL-6 levels in the serum. We correlated the clinical parameters and the neutrophil function.

Results: The average number of symptoms and the quality of life and functioning were significantly worse in the LCS Group. There was a significant difference in the level of serum IL-8 of the resting and Zymosan stimulated cells. The phagocytosing capability of the LCS group was significantly worse than the control group's. The superoxide production in resting conditions was significantly lower in sick children. After stimulating the superoxide production with phorbol ester (PMA) or Zymosan, the neutrophilic granulocytes of the LCS Group were significantly more hyperactivated than those of the control group. We revealed a negative correlation between the number of symptoms and superoxide production of the sick children.

Conclusions: According to our results, immunological dysregulation may be part of the immunopathogenesis of pediatric long COVID syndrome, with impaired superoxide production and phagocytosing capability of the neutrophil granulocytes. This could be a complication of the disease or part of a predisposing phenotype.

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Low birth weight associated with severe COVID-19 in children older than one year

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Background: According to the World Health Organization, more than 20 million babies are born annually with a low birth weight (LBW) of less than 2500 grams. LBW is an independent risk factor for cardiovascular diseases. Patients with a high cardiovascular risk or established cardiovascular disease have a higher risk to develop severe COVID-19.

Aims: Our aim was to investigate whether LBW can be associated with severe COVID-19 in children older than one year.

Methods: In our single-center observational study, 325 COVID-19 patients hospitalized between September 1, 2020, and July 31, 2022 were identified. After excluding infants aged < 1 year, data from 213 patients were retrospectively collected. A total of 142 children with available birth weight data were enrolled in our study. Fisher's exact test was used to assess the ratio of LBW among admitted patients compared with the regional incidence. The Kaplan-Maier method and Cox proportional-hazards model were used to test the relationship between the length of hospital stay and birth weight.

Results: LBW children were significantly overrepresented (12.58% vs. 8,37% regional, p = 0.0464*) among the patients required hospital admission. LBW was also associated with a significantly longer hospital stay (+3 days median value, p = 0.00083*). Neither obesity (p = 0.094) nor chronic conditions including chronic kidney failure (p = 0.16), chronic liver disease (p = 0.7), cystic fibrosis (p = 0.15) or developmental disorders (p = 0.086) had a significant association with the length of hospital stay.

Conclusions: Our results showed that LBW is associated with a higher probability and longer hospital stay. We conclude the LBW may contribute to the development of severe COVID-19 in pediatric patients.

Smell and taste disturbances in children with long COVID: A prospective, single center registry analysis

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Background: A significant proportion of children who had been affected with SARS-CoV-19 have reported experiencing a variety of sensory impairments including taste and smell disturbances, which can persist or develop after recovery from the acute infection, known as long COVID. Studies differ on the reported prevalence of these disfunctions (4.7-84.0%), which might be associated with malnutrition and even depressive symptoms, playing a key role in their quality of life, with no clear guidance on management.[1,2]

Aims: To investigate the prevalence and permanence of smell and taste disturbances after COVID-19 on children with the additional assessment of associated weight loss, quality of life (functioning), rate of therapeutical adherence, and its self-reported efficacy (odds ratios for reporting "improved" or "same" or "worsened" symptoms).

Methods: A registry analysis (March 2021 to, September 2022) was performed among 348 children (mean age: 12.14±4.08 years; 43.4% male) with confirmed preceding COVID-19 at the Long COVID Outpatient Clinic, 1st Department of Pediatrics, Semmelweis University, Budapest.

Results: The prevalence of smell disfunctions was 39.9% at the acute infection, and 26.4% at the time of first visit. The prevalence of taste disfunctions was 33.0% at the acute infection and 23.3% at the first visit. Only four (7.8%) children had persisting smell and five (9.8%) had taste problems after one year. The rate of weight loss among patients with smell disturbances at the first visit was 29.5% and 32.7% for those with taste problems. There is a significant connection between the presence of taste problems and weight loss (p=0,0056). Children with taste disturbances reported the worst mean overall functioning scores of 23.8 out of 48 and the highest change compared to before COVID-19 (6.8 out of 12 – the highest the score the highest the problem). The self-reported rate of utilization of any therapy was 42%. The odds ratio for reporting improved symptoms after one months of the recommended combined therapy of smell training, momethasone nasal spray and A-vitamin drops (12 children) compared to no therapy (28 children) was 10.11 with a 95% Confidence Interval of 1.05-97, p=0,045.

Conclusions: The prevalence of taste and smell disturbances were high amongst children affected with COVID-19, it but decreased considerably over the observed one year. Children with taste disturbances had the worst functioning scores with a higher chance for weight loss compared to non-affected peers. Although there is a tenfold chance for improved symptoms after one months of combined therapy, therapeutical compliance was low.

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Investigation of the protective effect of Human Milk Oligosaccharides (HMO) in bacterial endotoxin-induced fever

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Background: Sepsis - often caused by Gram-negative pathogens - is one of the most common causes of neonatal mortality. Oligosaccharides in breast milk (human milk oligosaccharides: HMO) are biologically active substances that may play a protective role in systemic inflammation.

Aims: The aim of our study was to investigate the potential antipyretic effect of different HMOs in bacterial lipopolysaccharide (LPS)-induced fever in mice.

Methods: Mice were implanted with intraperitoneal cannula after two weeks of habituation. Prior to induction of fever, different HMOs dissolved in physiological saline were administered intraperitoneally at equimolar doses. Two hours later fever was induced by the intraperitoneal administration of low-dose (120 µg/kg) LPS. Control groups received saline. The core temperature of the animals was recorded by thermocouples inserted into the colon at a thermoneutral ambient temperature.

Results: As expected, animals pretreated with saline showed a large temperature rise after LPS administration, peaking at 38.7±0.6°C 120 min after administration ($p<0.05$). Animals pretreated with two types of HMOs developed a significantly ($p<0.05$) attenuated fever response compared to control pretreatment, with maximum values of 37.5±0.4 and 37.6±0.3°C, respectively. No reduction in fever response was detected for the other HMOs tested ($p>0.05$).

Conclusions: Our results showed that the HMOs tested did not affect body temperature per se, but two of them significantly reduced the LPS-induced fever response, whereas no antipyretic effect was observed for the others. Our results confirm that breastfeeding is of paramount importance against bacterial infections, in which HMOs play a crucial role.

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Association of atherosclerosis with age, sex, overweight and adbominal thickness in caucasian cohort – autopsy study of 3400 subjects

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Background: According to the World Health Organization, cardiovascular disease is the leading cause of death globally, accounting for 17.9 million deaths per year. Atherosclerosis is a chronic disease that causes plaques to grow in the cardiovascular system and may impede blood flow. Even though more is known about atherosclerosis, there are still questions about the phenomenon. Autopsy studies of subjects who died of unnatural deaths, deliver a special chance to study atherosclerosis.

Aims: Our research aimed to conduct a cross-sectional study in a great Central European cohort to observe the possible relationships between arterial state, age, sex, body mass index (BMI) and abdominal thickness.

Methods: Altogether 3400 autopsy reports (n=2318 men, 68%; aged 0—96 years) have been collected for this study. All the cases were caused by unnatural death (suicide, homicide, accident). Pathobiological parameters such as BMI, thickness of the abdominal fat tissue and arterial state of six vascular regions have been collected. Arterial state were categorized in 5 subgroups (smooth endothel, fatty streak, fibrotic-, calcified- and ulcerative plaque) marked with atherosclerosis score (AS) 0 to 4.

Results: BMI drops from 1931 (22.82 kg/m^2) until 1947 (18.43 kg/m^2), followed by a rise, which reach its highest point in 2005 (27.88 kg/m2). Atherosclerotic degeneration begins in the abdominal aorta, followed by the thoracic aorta, the coronaries, the carotid arteries, the ascending aorta and finally by the cerebral arteries. Men experience statistically faster atherosclerotic deterioration in all blood vessels. The most rapid deterioration in both sexes was in the abdominal aorta. BMI over 25 kg/m^2 does not predispose statistical significantly higher AS neither in men nor in women. Logistic regression model revealed that regarding atherosclerosis age is the most important predictor, followed by sex, than BMI over 25 kg/m^2, and finally abdominal thicknesss.

Conclusions: This is the largest Central European autopsy study, covering six different vascular regions spanning nearly a century. In this study atherosclerosis begins in the first decade of life in both sexes, with the first degenerative changes occurring in the abdominal aorta. BMI over 25 kg/m^2 does increase the risk of atherosclerosis in every individual. The outcome of this study could be a potential clinical support for the healthcare professionals in the more personalized therapy, thereby reduce cardiovascular morbidity and mortality.

Case studies

Two cases of isolated proximal renal tubular acidosis caused by *SLC4A4* mutations

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Background: Inherited isolated proximal renal tubular acidosis is an extremely rare disease with unknown prevalence mostly caused by autosomal recessive mutations in *SLC4A4*, the gene encoding the basolateral sodium-bicarbonate cotransporter (NBCe1) and is characterized by renal bicarbonate losses without impaired reabsorption of other solutes in the proximal tubule. Patients exhibit specific phenotypic abnormalities which include severe hypokalaemic metabolic acidosis with normal anion gap, growth and mental retardation, glaucoma, cataracts, corneal opacities (band keratopathy), basal ganglia calcification, elevated serum lipase and amylase, dentition defects and migraine headaches.

Aims: Our aim was to compare laboratory and clinical phenotype of 2 paediatric patients with genetically confirmed proximal renal tubular acidosis.

Methods: We retrospectively analysed data from clinical, imaging and laboratory tests of 2 patients from 2 different centres, both with genetically confirmed isolated proximal renal tubular acidosis. We evaluated and compared type and extent of organ involvement as well as administered treatment and its efficacy.

Results: We described cases of 2 female patients (aged 5 and 7 years, respectively) with genetically confirmed proximal renal tubular acidosis caused by previously unreported mutations of the *SLC4A4* gene. In Patient 1 (5-year-old) was detected homozygous mutation c.392dupA (p.Ala132Glyfs*13) and in Patient 2 (7-year-old) heterozygous mutations c.1994_1997delTGAC(p.Asp665Glyfs*45) and c.2396A>C (p.Gln799Pro). Both patients presented in infancy with severe hypokalaemic normal-anion gap metabolic acidosis with subsequent need for massive alkali substitution. A common feature of the two patients is normal mental development, glaucoma, and zonular keratopathy with the need for repeated surgical interventions. Cataracts or intracerebral calcifications have not yet been proven in any of them. Both patients were recently started on novel treatment with potassium citrate and potassium hydrogen carbonate in the form of prolonged-release granules, but metabolic acidosis in Patient 1 still remains very difficult to correct. Her severe growth retardation does not respond to growth hormone treatment. At the age of 4, she suffered an attack of acute pancreatitis with constant increase of serum pancreatic enzymes until today. Dentition defects are present in Patient 2, in whom we also observe a better compensation of metabolic acidosis.

Conclusion: Due to the extreme rarity of the disease, larger data are needed about the prognosis and optimal management of patients with inherited isolated proximal renal tubular acidosis. Data comparison from larger group of patients could be beneficial in improving treatment and long-term outcome of these patients, which, however, will require broad international cooperation.

Temporally targeted interactions with pathologic brain oscillations as therapeutical targets in neuropsychiatric disorders

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Introduction: Existing drug therapies cannot ensure seizure-free life to one-third of the patients suffering epilepsy. Surgical interventions have very limited applicability, as they require well-defined, resecable seizure foci. Conventional transcranial electric stimulation (TES) can induce only subtle changes in neuronal activity and cannot promptly abrupt robust brain network patterns. Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy that typically begins in infancy or early childhood. It is characterized by difficult-to-treat seizures and is often resistant to therapy. Children with the disease may develop cognitive dysfunction, delays in reaching developmental milestones, and behavioral problems. If drug therapy does not respond or is untreated, the associated psychiatric symptoms may also become resistant to treatment or show a progressive tendency.

Methods: We showed earlier that non-or minimally invasive, closed-loop TES applied with proper intensity and temporal pattern can terminate epileptic seizures in animal models. Intersectional Short-Pulse Stimulation (ISP), our patented TES method, is capable of delivering high-intensity electrical impulses aligned to the ongoing brain rhythms with millisecond precision. We performed ISP stimulation of patient with Lennox–Gastaut syndrome through subgaleal electrode strips. Closed-loop stimulation was applied driven by a proprietary seizure detection algorithm.

Results: We found that 25 mA ISP stimulation could instantaneously terminate the overwhelming majority of the electrographic seizures (i.e. 33 of 39) during sleep, without waking the patient up.

Conclusions: Our results suggest that time-targeted ISP stimulation is a powerful tool for intervening pathological oscillations of epilepsy and possibly other neuropsychiatric disorders in humans.

When VZV goes beyond the skin: Adie syndrome

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Keywords: Adie syndrome; anisocoria, tonic pupil; varicella-zoster virus.

Background: Chickenpox is a very common childhood illness caused by varicella-zoster virus (VZV). The most cases of chickenpox are self-limiting and resolve without complications, but there are some very rare neurological and ophthalmic complications that can occur (Adie syndrome (tonic dilated pupil) and keratouveitis).

Aim: Present the potential ophthalmic complications that can arise from VZV infection.

Methods: 6-year-old girl was presented with anisocoria and redness of the left eye. At the same time, the child was suffering from chickenpox and the eye symptoms started on the fourth day of the typical rush. A complete ophthalmological and neurological examination was performed, including convergence testing and the visual acuity test. The child had brain and orbit magnetic resonance imaging (MRI) due to anisocoria to exclude some intracranial pathology. The girl was treated with systemic acyclovir for 7 days and topical steroid drops with tobramycin in her affected left eye. Keratouveitis was recovered, but anisocoria persistent with mild hypermetropia.

Results: Adie syndrome was diagnosed on the base of the next symptoms: left mydriasis (tonic pupil), absent light reaction, reduced visual acuity and poor conjunctival stimulus on the left eye. Ophthalmological examination also showed redness in affected eye, which indicates keratouveitis.

Conclusion: Adie syndrome is a rare but important diagnosis to consider in patients with pupillary abnormalities and a history of viral illness, so common in young children. Prompt recognition and treatment of these conditions can prevent potential long-term complications and improve overall vision outcomes.

Oncology, transplantation

Analysis of NTRK expression in childhood rhabdomyosarcomas

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Introduction: Rhabdomyosarcoma is the third most common extracranial solid tumour in childhood. Treatment of patients is multimodal; based on surgery, chemotherapy, and radiotherapy. The survival rate for patients with metastatic disease in the high-risk group is about 30%. For this reason, new therapeutic alternatives are needed.

In recent years, fusion aberrations in the neutrophin tropomyosin receptor kinase (NTRK) 1-3 genes have been detected in several pediatric tumours. The advent of specific NTRK inhibitors provides an opportunity of targeted therapeutic treatment of patients carrying these fusion proteins using NTRK inhibitors.

Objective: The aim of our study was to analyse the NTRK fusion profile of histological specimens from patients with rhabdomyosarcoma treated at the Department of Pediatrics No. II at Semmelweis University from 2007 to 2022.

Methods: Immunohistochemical assay was performed on sections from paraffin-embedded histological blocks. NTRK proteins expressed by tumour cells were detected using anti-pan-TRK antibody. The stained sections were digitized using a scanner and then analysed for expression levels and cellular location of the protein using CaseViewer software.

Results: A total of 45 patient samples were analysed. Of the samples examined, 31 were embryonic, 8 were alveolar and 6 were of other histological subtypes. Based on the risk classification of the CWS 2012 protocol, two thirds of the patients studied belonged to a high or very high risk group. The presence of NTRK fusion protein was confirmed in 17 cases. The protein typically showed a cytoplasmic appearance in the cell, and in many cases nuclear or membrane positivity was seen in addition to cytoplasmic staining.

Conclusions: Our study showed the presence of NTRK fusion protein in 38% of the cases studied. Following confirmation of these findings by genetic testing, these patients could be potential candidates for NTRK inhibitor treatment in case of relapse.

Conventional and targeted therapies in pediatric oncology: Efficacy and adverse events

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Background: Pediatric oncological treatment places a great burden on families, healthcare and economy globally. Conventional therapies (such as surgical resection, chemotherapy and irradiation) bring on both short and long-term side effects which can be detrimental.

Personalized (targeted) therapies improve outcomes in high risk patients as per the MAPPYACTS trial in 2022.

Targeted therapies could enhance survival with an acceptable side effect profile.

Aims: Our primary aim was to estimate the additional therapeutic effect of targeted therapeutic modalities (including, monoclonal antibodies and small molecule drugs) compared to conventional methods in pediatric oncology (comparative studies). Our secondary aim was to analyze all pediatric oncology studies focusing on targeted therapies (non-comparative studies).

Methods: We conducted a systematic search on the 13th of October 2021, in MEDLINE, Embase, CENTRAL, Scopus and Web of Science databases. Out of 23343 hits and 17786 articles remaining after duplicate removal, we found 236 eligible studies.

Upon analyzing the survival outcomes for pediatric patients treated with conventional therapies alone (control group) versus conventional therapies with additional personalized treatments (interventional group), we estimated the survival benefit of additional targeted treatments. Additionally we compared the number of side effects between patients receiving targeted therapies only versus targeted therapies in combination with chemotherapy.

Results: The event-free survival probability significantly favored the interventional group at 5 years follow-up time. Upon comparing the hazard ratios for events, the targeted therapy group showed significantly improved likelyhood for event-free survival (HR=0.82, p=0.08). The overall survival also favored the interventional group. Upon examining the hazard ratio for mortality in the two groups, we could see a significant benefit of targeted therapy for survival. (HR=0.79, p=0,03).

The number of adverse events in the non-comparative studies were not statistically significantly different between the targeted therapy only group versus the targeted therapy and conventional therapy group.

Conclusions: Overall survival is significantly improved by the addition of targeted therapies in pediatric oncology, especially in hematological malignancies. However, solid tumor studies are underrepresented and more randomized controlled studies are needed for an accurate estimation of additional targeted therapeutical effect.

Monitoring longitudinal changes of the comlement activity during allogeneic stem cell transplantation- early raise of the sC5b-9 activation marker is predictive for later development of TA-TMA

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In thrombotic microangiopathies (TMA), the role of complement dysregulation has been well evaluated, but it remained less understood in secondary TMAs. We aimed to analyze longitudinal changes of the complement profile after allogeneic hematopoietic stem cell transplantation (HSCT) in a prospective, consecutive pediatric cohort, and we aimed to understand the role of these changes in the transplantation associated (TA) complications. This work summarises the results of our original and validation cohort together.

Patients and Methods: We enrolled 33 pediatric patients in the first (2013-September 2015) and 67 pediatric patients in the second (October 2015-January 2019, validation cohort) study period who underwent allogeneic HSCT. Five different TA-TMA diagnostic criteria were applied, and all important clinical and laboratory parameters of TA-TMA activity were registered. Complement pathway activities, components and sC5b-9 levels were systematically measured before and on day 28, 56 and 100 after HSCT.

Results: Overall 10/33 and 10/67 subjects met at least one of the different TA-TMA diagnostic criteria according to the five classification systems, typically on day 61 and 62 (median, range: 16-98 and 35-90). We identified sC5b-9 as the most potential complement biomarker of TA-TMA development. A strong and remarkable association have been found and this observation has been validated between early increase of sC5b-9 (from pre-tx baseline to day 28) and later development of TA-TMA. This increase had a sensitivity of 100% and a specificity of 61% and 53% in the original and validation cohorts. After reduced toxicity conditioning regimen, in majority of patients (N=15/20) TA-TMA was mild and self-limiting, without any signs of organ damage. No additional complement parameters were closely associated with the development of TA-TMA. Surprisingly, grade I to II graft-versus-host disease had almost the same incidence as TA-TMA after reduced toxicity conditioning regimen. Furthermore, all TA-TMA cases have been observed during or after cyclosporine immunosuppression.

Conclusions: We firstly evaluated the longitudinal changes of the comlement system during HSCT. We validated our observation, that early raise of the sC5b-9 activation marker is predictive for later development of TA-TMA. In patients with a marked increase, early and frequent monitoring of TA-TMA activity markers should be attempted, to facilitate therapy decisions in time. Further studies enrolling higher number of patients are necessary to determine the role of immunosuppression and the conditioning regimen in the pathogenesis of TA-TMA.

Gastroenterology, surgery

The frequency of new extraintestinal manifestations in patients with inflammatory bowel disease on second generation drugs: A systematic review and meta-analysis

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Background: Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis is a chronic, relapsing-remitting disorder of the gastrointestinal tract. Extraintestinal manifestations (EIM), mostly affecting the joints, skin and eyes, are frequent (10-25%) and have a negative impact on the quality of life of patients with IBD, they need to be considered during therapeutic decisions. Anti-TNFs revolutionized the management of IBD, however, approximately 30% of the patients experience loss of response. In these cases new biologicals and small molecules are available, some of them are gut-selective, other are indicated in immune-mediated diseases that can occur as EIMs in IBD. Currently, there is no evidence which drug should be recommended in patients with EIMs.

Aims: Our aim is to investigate the occurrence of new EIMs and the proportion of improvement/worsening of pre-existing EIMs in patients with IBD treated with non-TNFi biologics or small molecules.

Methods: We conducted a systematic literature search in EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials and Web of Science on November 15, 2022. We enrolled studies reporting on the occurrence and behaviour of EIMs in patients with IBD receiving advanced therapy. To analyse our question proportion of new, worsening and improving EIMs were calculated with 95% confidence intervals (CI). The protocol of the study was registered with the National Institute for Health Research PROSPERO system under the registration number CRD42022366812.

Results: Altogether 13544 articles were identified, after the selection 68 studies were found eligible for the analysis, covering 14726 patients. The most frequent EIM was joint involvement. We formed subgroups based on the applied drugs. The proportion of new EIMs was 8% (95% CI, 0.05-0.13) in the ustekinumab group and 9% (95%CI, 0.01-0.23) in the vedolizumab group, the heterogeneity was high (I^2=92% and 86%) The improvement of pre-existing joint involvement was 40% (95%CI, 0.35-0.46) in case of vedolizumab, 50% (95%CI, 0.38-0.62) in the ustekinumab group and 48% (95%CI, 0.32-0.65) in patients treated with upadacitinib. 14% (95%CI, 0.03-0.33) of pre-existing joint involvement worsened during vedolizumab treatment, whereas it was 4% (95%CI,0.01-0.15) in

patients receiving ustekinumab. The final statistical analysis regarding the other EIMs is in progress.

Conclusions: According to the preliminary analysis, there is no significant difference in the impact on EIMs between gut-selective and systematic advanced drugs in patients with IBD. The final conclusion can be drawn after the whole statistical analysis has been completed.

Detection of AIRE, POLE2 and CARMIL2 gene mutations and hypogammaglobulinemia in two VEO-IBD patients: a comparative case report

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Background: Very Early Onset Inflammatory Bowel Disease (VEO-IBD) is defined as IBD presenting before 6 years of age. Research shows that VEO-IBD often has an underlying monogenic etiology and is associated with primary immunodeficiencies (PID). Since the prevalence of VEO-IBD has increased significantly in the past years, there is a growing need to understand the underlying causes behind this disease, in order to be able to provide more targeted treatment options. Next-generation sequencing has been proven to be an effective approach to evaluate PIDs.

Case report: We present two cases of VEO-IBD. The first patient was a 14-month-old boy who had been recently diagnosed with Systematic Juvenile Idiopathic Arthritis (SJIA). He was treated with steroids, methotrexate and tocilizumab, but despite the combined immunomodulant treatment, he started to have symptoms such as failure to thrive, weight loss, bloody diarrhea. He was ultimately diagnosed with VEO-IBD secondary to mutations in the AIRE, POLE2 and CARMIL2 genes, with no clinical signs of immunodeficiency.

The second patient was a 3-month-old girl presenting with hematochezia refractory to 6-food elimination diet and recurrent enteral sepsis. Immunological examination proved hypogammaglobulinemia, later the endoscopy and histology confirmed the diagnosis of IBD, but unlike the other case, with no identifiable genetic mutations in the background. She receives immunoglobulin replacement and since then she's been in complete clinical remission.

Both patients were genetically tested with NGS, but the results seem to be not entirely conclusive with the clinical manifestations. Ongoing studies and case presentations show that there is a growing number of identified novel genetic defects underlying PIDs and VEO-IBD, but identifying genetic defects in these patients is still challenging and there is a lot more to uncover.

Conclusions: As of now, the successful identification of monogenic etiologies behind VEO-IBD happens in about 20% of all cases, but our cases show that sometimes immunology and genetics don't align with each other. NGS and further genetic research can help with these complex cases and therefore initiate the use of alternate and targeted therapies.

Risk factors for early intestinal resections in pediatric Crohn's disease

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Background: Based on clinical experience, there are some children with Crohn's disease (CD) who's CD starts in sever form or the induction therapy is ineffective. Therefore, they require intestinal resection shortly after diagnosis. Intestinal resection can cause vitamin deficiencies. There is a high chance of further resection which can easily lead to short bowel syndrome. Moreover, patients may require a stoma. All of this have a major impact on patient's quality of life.

Aim: The aim of our study was to characterize this patient group and identify risk factors which associated with early intestinal resections.

Methods: We performed a retrospective analysis based on the database of the Hungarian Pediatric IBD Registry (HUPIR). The HUPIR is a prospective, nationwide registry launched in 2007. Data of patients under 18 years of age who were diagnosed with CD between 2010-2019 and underwent intestinal resection within six months after diagnosis were compared to children with CD who did not require resection within six months. We sought to answer whether diagnostic delay, age, sex, pediatric Crohn's disease activity index (PCDAI), extraintestinal manifestations, perianal involvement, upper gastrointestinal involvement and abdominal pain without diarrhoea influence the incidence of early intestinal resection. Descriptive statistical methods were used for data analysis.

Results: Altogether 1040 newly diagnosed CD patients were reported between 2010-2019, among them 27 required intestinal resection within six months after diagnosis. The mean age at diagnosis among those who underwent early intestinal resection was 14.9 (8.9-17.5) years, compared to 13.7 (0.92-18.0) years in the non-operated population. The time from onset of symptoms to diagnosis was shorter in the early surgery group (4.4 (0-38.5) month) than in the control group (7.0 (0-82.2) month). 63.0% were women and 37.0% were men in the early resection group. PCDAI was higher among those requiring intestinal resection within six months (38.6 vs 29.2). Perianal involvement and abdominal pain without diarrhoea were more prevalent in the group of children who underwent early surgery, while a lower percentage of extraintestinal manifestations were observed in this group.

Conclusion: Patients who required early surgery had a higher PCDAI and a shorter delay in diagnosis, suggesting that these patients may have a more rapid and severe onset of disease. Abdominal pain without diarrhoea may delay the diagnosis. More frequent perianal involvement highlights the importance of examining this region.

Biomechanical comparison of different K-wire fixation methods for the treatment of pediatric distal radius fractures on 3D printed bone models

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Background: Distal forearm and wrist fractures are the most common pediatric fractures, where K-wire fixation is the most widely used operative method. However, there is still a controversy regarding the number of wires and site of insertion in the literature. The study aims to critically compare the biomechanical stability of different K-wire fixation techniques.

Aims: The study aims to critically compare the biomechanical stability of different K-wire fixation techniques.

Methods: Different osteosyntheses were reconstructed on 189 bone models under a novel, standardized conditions. The model was created using 3D printing and molding techniques. The simulated fracture was fixed with two K-wires inserted from radial and dorsal directions (crossed wire fixation) or both from radial direction, in parallel (parallel wire fixation). Single wire fixations with shifted exit points were also included. 3-point bending tests with dorsal and radial load have been carried out. Torsion tests have been also performed.

Results: We measured the maximum force required for a 5 mm displacement of the probe under dorsal and radial loads (crossed wire fixation.: 249.49 N and 355.89 N; parallel wire fixation.: 246.36 N and 308.27 N; single wire fixation: 115.86 N and 166.46 N; on average; n=27 in all cases). We also measured the torque required for 5º and 10° torsion, which varied between 0.15 Nm and 0.36 Nm; on average; n=27 in all cases).

Conclusions: The crossed wire fixation provided the most stability during the 3-point bending tests. Against torsion, both the crossed and parallel wire fixation were superior to the single wire fixations. Proximal shift of the K-wire's exit point resulted in greater stability under radial load and torsion, but lesser stability under dorsal load.

The presented novel method is suitable for the standardized evaluation of different fracture fixing methods. According to the findings, crossed wire fixation potentially withstand greater bending, tilting forces after operation. Against torque forces, single wire fixation showed the less resistance. The observations can support clinical decision-making and preoperative planning as well.

Poster abstracts

PI-01

The effect of Covid-19 pandemic on the care of neonates with hypoxic-ischemic encephalopathy

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Background: The Covid-19 pandemic had a severe impact on many non-infectious areas of the healthcare system. Neonates born with asphyxia require urgent intervention where access to early and proper intervention is essential for the best possible outcome. During the lockdown, people had limited ability to access emergency healthcare and also for hospital visits.

Aims: To compare the indicators of short-term outcome of asphyxiated neonates treated for hypoxic ischemic encephalopathy (HIE) during the Covid-19 pandemic and before the pandemic.

Methods: This was a retrospective, registry-based cohort study conducted at the Level III Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Semmelweis University. Patients who were born between 2018-2022 and received therapeutic hypothermia were recruited to the study. Patients were divided into two groups: (1) Pre-Covid era patients were born between 03.2018-02.2020; (2) Covid era patients were born during the lockdown in Hungary, between 03.2020-02.2022. Statistical analyses were performed using parametric or non-parametric test as appropriate with a significance level of $p<0.05$.

Results: 127 patients were assigned to the Covid era group, and 115 patients were assigned to the Pre-Covid era group. We did not see a change in the number of asphyxiated neonates referred for tertiary care. In addition, the baseline clinical characteristics were similar in the two study periods. In the Covid group, 72/127 (57%) patients were born via emergency C-section, and 63/115 (55%) in the Pre-Covid group. The 5-minute Apgar score of the groups were similar (Covid: 4.9±2.5, Pre-Covid: 4.7±2.7, p=0.485). Initial blood gas parameters were also comparable, and hypothermia was initiated early in both periods (Covid: median 2.3 [IQR 1.4; 3.8]; Pre-Covid: 2.8 [1.8;4.3] hours of life). The length of NICU stay was not different either (median 8.5 vs 9 days, respectively, p=0.499). Importantly, during the Covid era, fewer patients were discharged from the NICU with breastfeeding or bottle feeding (Covid: 54/127 [42%], Pre-covid: 65/115 [56%], p=0.039).

Conclusion: Covid-19 pandemia did not have a significant effect on perinatal events or NICU length of stay, however, we observed a decrease in breastfeeding/bottle feeding. We suggest that even at challenging times, attention should be given to parents to allow sufficient time to spend with their newborns.

PI-02

Effect of SARS-COV-2 mRNA vaccination on hemostasis and disease activity in children with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), are associated with higher thrombotic risk and enhanced thrombin generation (TG) in adults. IBD patients were underrepresented in SARS-CoV-2 mRNA vaccine trials. Case reports indicated that adverse events post-vaccination, including IBD flare, were more common among children, and those with prior COVID-19.

Aims: To find out whether TG is increased in children with IBD as compared to healthy controls and whether TG parameters show significant changes following SARS-CoV-2 mRNA vaccination.

Methods: In this observational case-control study, 37 children with IBD (CD:16, UC: 21) aged 12-18 years and 55healthy age-matched children were enrolled. Blood was collected before and 2-4 weeks after the second dose of BNT162b2 (Pfizer-BioNTech) vaccine dose. Whole blood count, fibrinogen, inflammatory markers (CRP, ferritin), anti-SARS-CoV-2 antibody levels were investigated, TG assay was carried-out using platelet-poor plasma. Lag time, endogen thrombin potential (ETP), peak thrombin, time-to-peak were calculated. Detailed clinical parameters including post-vaccination symptoms, COVID-19 history, disease activity scores (PUCAI, Mayo score, PCDAI) were registered.

Results: CRP was significantly elevated in children with IBD and showed a positive correlation with ETP (CD: r=0.700; p=0.003 and CU: r=0.501; p=0.020). TG parameters did not differ between patients and controls pre- or post-vaccination. TG parameters remained unaltered post-vaccination in both groups. IBD disease flare was not observed post-vaccination, but reduced anti-SARS-CoV-2 antibody titers were found in 4patients receiving immunosuppressive therapies. Previous COVID-19 infection had no effect on TG levels.

Conclusions: Although TG parameters correlated with the level of inflammation in children with IBD, the extent of TG was not significantly different from healthy controls. TG parameters and IBD disease activity scores did not increase significantly following mRNA vaccination. Our results support the safety of SARS-CoV-2 mRNA vaccination in children with IBD, highlighting observations of lower antibody titers in immunosuppressed children.

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PI-03

What is responsible? Genetics, anatomy, pregnancy or COVID-19?

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Introduction: Deep vein thrombosis (DVT) is the most common thrombotic event in childhood. There is currently limited evidence available in pediatrics on the role of diagnostic biomarkers for determining the probability of DVT. Until recently, D-dimer was the mostly used biomarker for this. As there is a close correlation between SARS-CoV-2 infection and coagulopathy, the COVID-19 pandemic has significantly limited the clinical utility of laboratory tests.

Case report: A 15-year-old girl was admitted to the hospital with back pain lasting for two weeks without any other complaints or symptoms. The day before, she underwent an artificial abortion and she was also tested positive for SARS-CoV-2 infection. Based on the history, symptoms and negative physical examination, orthopedic and neurological diseases were considered during the differential diagnosis. Orthopedic and neurological examination did not reveal any abnormality; therefore, after a negative abdominal ultrasound, a lumbosacral and pelvic MRI was performed to rule out space-occupying lesions of the spine. The MR image raised the possibility of DVT, which was later confirmed by Doppler ultrasound. The imaging studies described a circular thrombus completely filling the lumen in the left popliteal vein, the common femoral vein on both sides, and the inferior vena cava up to the umbilicus, with detectable circulation. After the diagnosis, abnormally elevated D-dimer level was detected and low molecular weight heparin (LMWH) treatment was started. One week after the ultrasound confirmed diagnosis, abdominal MR identified May-Thurner syndrome. Although the rare anatomical anomaly may justify the more significant extension of the thrombus on the left side, it does not explain the size of the thrombosis. After 14 days, our patient was discharged without complaints. Tests for thrombophilia are in progress.

Conclusion: (1) If the thrombus slowly and chronically narrows the circulation, even the complete blockage of the veins does not necessarily cause significant symptoms. Therefore, if DVT is suspected, do not reject the diagnosis even in the absence of obvious clinical signs. (2) D-dimer level determination is of limited value in the diagnosis of childhood thrombosis. In addition, its serum level often rises during concurrent viral infections, especially SARS-CoV-2 infection, so it is not routinely determined due to its non-specificity. If thromboembolism is suspected, only the imaging studies can lead to definitive diagnosis.

PI-04

Most frequently detected respiratory pathogens in patient samples during pre-COVID, COVID and post-COVID periods (January 2018 to February 2023)

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Background: We were curious of the pathogen incidence pattern during the pre-COVID (before February 2020, COVID (February 2020-April 2022) and post-COVID (after March 2022) periods in the patients' samples. We analyzed the microbial culture results from the laboratory information system.

In parallel we summarized the available SARS-CoV-2 RT-QPCR results, *in vitro* molecular syndromic results (BioFire® FilmArray® 2.0 System), lateral flow antigen rapid test results (SARS-CoV-2, Influenza A, Influenza B, Adenovirus, RSV).

Aims: The aim of this study was to evaluate the occurrence of different pathogens during pre-COVID, COVID and post-COVID periods in patient samples admitted to the Central Laboratory, Heim Pál Children's Hospital, Budapest, Hungary, using different diagnostic methods.

Methods: Respiratory sample results of the patients from January 2018 through February 2023 which admitted to the Central Laboratory were analyzed. A retrospective cross-section study was fulfilled on microbial culture results (12 685), *in vitro* molecular syndromic results (331), SARS-CoV-2 RT-QPCR (27 823), lateral flow rapid test results (71 684).

Results: During the above mentioned COVID-related periods the following emphasized pathogens' prevalence noticed to remarkable in the diagnostic and further epidemiological viewpoint. The overall respiratory sample number were 12 685 from January 2018 through February 2023, although, the amount increased by 8.5 % from 4 909 (pre-COVID) to 5 328 (COVID). The number of bacteria and fungi positive respiratory sample in microbial culture was increased by 21%.

The undermentioned microorganisms incidence increased by 206% for the *Candida parapsilosis*, by 117.5% for the *Klebsiella pneumoniae*, by 81% for the *Proteus mirabilis*, by 63% for the *Candida albicans* and decreased by 59% for the *Haemophilus influenzae*, decreased by 50.5% for the *Streptococcus pneumoniae*, decreased by 80% for the *Streptococcus pyogenes* when compared to pre-COVID.

The post-COVID period (11 months) duration too short for further comparison to the pre-COVID and COVID periods respectivelly, although the positivity of *H. influenzae, S. pneumoniae, S. pyogenes* are noticeable.

SARS-CoV-2 RT-QPCR and antigen CoV-2 rapid test positive results implied not be related to certain bacterial or fungal positivities.

In vitro molecular syndromic results showed that the most frequently detected pathogens were the following, Human Rhinovirus/Enterovirus; *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.

Influenza A rapid test positivity rate in 2022 Q1 and 2023 Q1 were 23.7% and 26.3% respectively.

RSV rapid test positivity rate 42.8% occurred since January 2023.

Conclusions: Few remarkable pathogens incidence notably increased or decreased during COVID, compare to pre-COVID period. Influenza A and RSV incidence is strongly conspicuous in post-COVID period.

PI-05

Abused health-care workers in a child and adolescent psychiatry setting: what are the risk factors?

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Keywords: multicausal model, doctor-patient relationship, high security psychiatry, workplace violence, relatives in psychiatry, debriefing

Background: Violence against healthcare workers (VAHCW) is defined as a situation in which a healthcare worker is subjected to physical or psychological abuse in the workplace. Some of these may be officially prosecutable offences and others may be investigated in private charges. There are criminological and psychiatric reasons behind the VAHCW. It seems that in Hungary this is mostly dealt with by the press, and it is also striking that these events are not reported by staff. The risk factors for VAHCW are divided in the international literature into three more or less distinct groups: patient-related, external causes and situation factors. Research based on qualitative methodology has also addressed this phenomenon. Children and adolescent psychiatric patients and their relatives are not exceptional, they can be also violent.

Aims: Psychiatry is a dangerous setting that requires an extraordinary effort from the staff. Healthcare workers in psychiatry are exposed to significant levels of violence. Identifying the risk factors of abuse is a social concern. We explored and identified the criminological and psychiatric causes of VAHCW in a child an adolescent psychiatric emergency ward in Budapest, Hungary.

Methods: We used a semi-structured, self-developed, online questionnaire involving 21 respondents. The participants were representing the staff composition of our department. The data set was coded in two phases using a multi-stage content analysis method. The results were compared with Hungarian and international literature.

Results: 52% of the participants did not experience physical abuse. Threat was the most frequent (38%) type of perceived non-injury abuse. The most common risk factors of abuse were psychiatric disorder of the child, communication, parental behaviour and low socio-economic status. Psychological trauma was found to be the most common consequence. According to the opinion of the respondents, violence caused most often (52%) by the child's mental disorder. Workers were reported to cope with abuse mostly with negative emotions. 76% of them reported the victimization. 43% said that abuse cannot be avoided. 19% said that the competence of workers is important.

Conclusions: There is a well-defined reason why should focus on the importance of training, education and debriefing. Mindfulness is important for the prevention of VAHCW. Assertiveness is also a crucial factor in the immediate prevention of violence. Principles of confidentiality should not be at the expense of personal safety. Interpersonal contact between colleagues has an impact on the perception of children's aggressive behaviour. The perception of aggression is a continuum that is directly influenced by the group dynamics between staff members. Authoritarian and over-indulgent environments do not have a good effect on children with psychiatric illness. Individual and group-based clinical supervision integrated into the work schedule reduces burnout and moral distress. Discussing and sharing practice issues (debriefing) reduces anxiety, burnout, and the frequency of conflicts between staff members. Effective situational awareness, self-awareness, self-confidence, good time management, regular feedback, and the development of communication techniques are critical. Finally, it should be emphasised that a person working in a

psychiatric field should ideally be aware of their own fears, anxieties and sensitivities before taking up a helping occupation.

PI-06

A century-long overview of body weight, height and BMI value in the Southern Great Plain region of Hungary based on autopsy data

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Background: Overweight and obesity affect both adults and children, which condition represents a serious health, public health and social burden. Based on the World Health Organization data from 2016, the prevalence of obesity in Hungary is 72.8% among males and 59.0% among females. In the mentioned region, no comprehensive survey was previously carried out to describe the prevalence in the last century, however, we can obtain indicative data based on autopsy reports.

Aims: The purpose of our investigation is to study the development of typical body height, body weight and BMI data calculated from the last century.

Methods: The autopsy reports were available on request from the database of University of Szeged, Institute of Forensic Medicine from the population of the Southern Great Plain region. The data collection excluded data from deaths with natural causes alongside with people noted with mutilated body parts and included data from suicide, homicide, accident resulted deaths. Thus, 2603 adult autopsy report were evaluated between 1928 to 2010 (among which 1766 are male and 837 are female). Data were also divided to age groups as well. Statistical analysis was performed via two-way analysis of variance (ANOVA) with post-hoc Tukey test.

Results: Each investigated age group and sex distribution had significant effect on the body weight acquired from the data (***, $p < 0.0001$). Among the male population, the average body weight increased by 18.60 kg, whilst this was 9.36 kg among females. The same can be claimed about the body height, where the height increased with 8.63 cm and 6.0 cm for male and female population, respectively. The difference between the sexes also showed significant effect in each age groups (**, $p < 0.001$). According to post-hoc analyses, the calculated BMI values in the time interval 1990 to 2010 are significantly different from the previous eras for both male and female population (**, $p < 0.001$). In the time interval from 1990 to 2010, both sexes in certain age groups falls into overweight category based on their average BMI.

Conclusions: Our data shows that the average body height and weight has increased in the last century, and thus the average BMI for both sexes. With the increasing prevalence of overweight and obesity timely manner diagnosis and the recognition of co-morbidities and possible complications play an important role also in public health point of view.

PI-07

PARK7 as a new therapeutic target in pulmonary fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease characterized by excessive scarring, increasing breathlessness, and death within three to four years after diagnosis. Development of IPF is a result of an aberrant, repetitive alveolar epithelial injury, in which the oxidative stress plays a dominant role. Parkinson's Diseases 7 (PARK7) molecule is a central mediator of the antioxidant defence mechanisms of various organs, however, its role in IPF and the underlying mechanisms is still unknown.

Aim: In the present study, we aimed to investigate the role and therapeutic potential of PARK7 in IPF.

Methods: Pulmonary expression of PARK7 was investigated in the bleomycin induced mouse model of lung fibrosis. The effect of pharmacological PARK7 activation with Comp-23 on the synthesis of extracellular matrix (ECM) components, including collagen-1 (Col1a1) and fibronectin (FN) in the lungs was investigated *in vivo*. The effect of Comp-23 treatment on oxidative damage (H_2O_2, bleomycin) induced death of lung alveolar epithelial cells (A549) was investigated *in vitro*.

Results, and conclusion: We found increased PARK7 expression in the fibrotic lung of mice treated with bleomycin. PARK7 activation with Comp-23 treatment diminished the bleomycin induced Col1a1 and FN levels in the lungs. Comp-23 treatment decreased the H_2O_2 and bleomycin induced cell death of A549 cells. Our data suggest that PARK7 protects the alveolar epithelial cells against oxidative damage thereby reducing the pathologic alterations in the lung leading to the development of IPF. Therefore, PARK7 may serve as a potential therapeutic target in the treatment of IPF.

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PI-08

Targeting SGLT2 for renal fibrosis prevention: A promising therapeutic approach

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Background: Diabetic kidney disease (DKD) is a significant public health concern. Despite the widespread use of standard-of-care therapies, DKD remains the leading cause of endstage renal disease. Therefore, the identification of novel therapeutic strategies that reduce the risk of DKD is a research priority. Large clinical trials have recently shown that sodiumglucose cotransporter-2 (SGLT2) inhibitors improve renal outcomes beyond their glucoselowering effects. In diabetes, enhanced glucose reabsorption leads to tubular hypoxia, which triggers a fibrotic response. Hyperglycemia is strongly associated with increased protein *O*GlcNAcylation, which is a post-translational modification known to contribute to the development and progression of renal fibrosis.

Aims: Given the involvement of proximal tubules in the pathogenesis of DKD and the key role of SGLT2 in glucose metabolism, here we investigated the effects of SGLT2 inhibitors on tubular hypoxia and *O*-GlcNAcylation.

Methods: Diabetes mellitus (DM) was induced in adult male Wistar rats by streptozotocin (65 mg/bwkg, *ip.*). Following the onset of DM, the rats were treated with dapagliflozin for six weeks (D+DAPA, 1 mg/bwkg/day, *po.*). Metabolic parameters, renal function, novel urinary biomarkers of extracellular matrix remodeling, and histology were evaluated. In addition, the effect of hyperglycemia was tested in human proximal tubular epithelial cells (HK-2) under normal glucose (5.5 mM), high glucose (35 mM), or high mannitol (osmotic control, 35 mM) conditions for 24 hours. To test hypoxia, cells were placed in a hypoxic chamber (1% O_2, 2h) and treated with 10 μM DAPA.

Results: DAPA decreased blood glucose levels (DM: 37±2.7 *vs.* DM+DAPA: 18±5.6 mmol/L; $p<0.05$) and improved renal function as evidenced by an increase in creatinine clearance (DM: 3.8±0.4 *vs.* DM+DAPA: 8.9±1.0 mL/min; $p<0.01$). Additionally, DAPA treatment led to a reduction in novel urinary biomarkers of extracellular matrix remodeling (Pro-C3, uC3M, tumstatin), profibrotic growth factor expression (*Tgfb, Pdgf, Ctgf*), and extensive fibrotic tissue accumulation in the kidney. In HK-2 cells, DAPA treatment minimized hyperglycemia-induced total protein *O*-GlcNAcylation and suspended hypoxia-induced HIF-1α elevation. Furthermore,

DAPA treatment prevented HIF-1α translocation to the nucleus, thereby confirming abolished HIF-1α activation. Finally, DAPA treatment prevented *EPO*, *TGFB*, and *PDGF* elevation in hypoxic conditions.

Conclusions: This study highlights the important benefits of SGLT2i treatment in ameliorating *O*-GlcNAcylation and reducing tubular hypoxia. Our findings support the link between glucose toxicity, tubular hypoxia, and fibrosis, which appear to be targeted by SGLT2 inhibitors. These results enhance our understanding of the complex system underlying the renoprotective effects of SGLT2 inhibitors in DKD.

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PI-09

Gender-specific differences in cystic kidney disease progression and treatment response in PKD/Mhm rats

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Background and aims: Cystic kidney disease is a rare group of diseases that damage the kidney tissue, causing hypertension, haematuria, and proteinuria leading to vascular damage. Renal failure is a long-term consequence and only symptomatic therapy is available. We investigated disease progression in older PKD/Mhm (Cy/+) rats, including endothelial function, and in parallel evaluated an anthelmintic drug's potential to intervene early in the disease in younger rats.

Methods: We used isolated rings of thoracic aorta from six-month-old heterozygous PKD/Mhm (Cy/+) female and male rats compared to age-matched healthy (+/+) controls to determine the contractile and relaxation responses *ex vivo* in the organ bath.

Cyst inhibitory drug (anthelminthic) identified by high content screening in zebrafish was applied to 3 weeks old male and female PKD/Mhm (Cy/+) rats for a total of 10 weeks to evaluate early drug effect on kidney and endothelial function. Untreated PKD/Mhm (cy/+) rats fed a normal ROD16 diet served as controls. Kidney function was assessed by transcutaneous measurement of FITC-Sinistrin. Size and number of cysts were examined histologically.

Results: Endothelial function was impaired in 6-months old male PKD/Mhm (Cy/+) rats compared to healthy control rats (+/+), shown by decreased maximal relaxation to acetylcholine compared with controls (55±2% vs. 77±1%, p>0.05). Contractile responses to phenylephrine (3.0±0.1g vs. 3.4±0.1 g, p>0.05) and high potassium (3.3±0.1 g vs. 3.7±0.1 g, p>0.05) were also lower in male PKD rats compared to male controls. These parameters were unchanged in PKD female rats compared to control females.

Preliminary results after 10 weeks of treatment with the anthelmintic showed an improvement in GFR in treated PKD females compared to untreated controls (t½: 0.24□0.06 vs. 0.51□0.16 min, p=0.02), but a worsening in males compared to untreated controls (t½: 0.93□0.49 vs. 0.48□0.12 min, p=0.02). Concomitantly, we found a decrease in serum urea and creatinine levels in male treated PKD rats compared to untreated controls (urea: 83.17±33.73 mg/dl vs. 62.40±13.79 mg/dl, p=0.05; crea: 0.84±0.35 mg/dl vs. 0.55±0.14 mg/dl, p=0.18). Ex vivo organ baths showed a tendency to worsen endothelial function in treated male PKD/Mhm (cy/+) rats, but not in females.

Conclusion: PKD/Mhm (cy/+) rats developed kidney failure and cysts regardless of sex. Associated endothelial dysfunction was observed only in male rats. Treatment with the anthelminthic improved renal function in female rats, but not in males. Strikingly, it even further aggravated kidney function and endothelial function. Therefore, the gender aspect should be considered when planning (clinical) trials.

PI-10

Origin of extracellular vesicles from peritoneal dialysate and their immunomodulatory effect

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Background and Aims: Due to their low immunogenicity and unique immunosuppressive properties, mesenchymal stem cells (MSCs) are considered one of the most promising cell types in human therapy. Furthermore numerous studies confirm the regenerative and anti-inflammatory properties of MSC derived extracellular vesicles (EVs). Our present aim was to investigate the possible stem cell origin and role of EVs isolated form the peritoneal dialysate (PDE) of patients with peritoneal dialysis (PD).

Methods: EVs were isolated from PDE using ultrafiltration and size exclusion chromatography. Following a quality check, Western blot was carried out to investigate the presence of stem cell -(CD75, CD90, CD105), endothel- (CD31), mesothel- (CK-18, E-Cadherin) and mesenchymal (fibronectin) markers as well as the absence of CD14, CD34 and CD11b immune cell markers on the isolated EVs. The effect of PDE-EV treatment on cytokine production of peripherial mononuclear cells (PBMCs) under physiological and pathological (inflammatory) conditions was investigated using RT-PCR and ELISA.

Results: Presence of stem cell marker CD105, mesothelial marker CK18 and E-cadherin and mesenchymal marker fibronectin was confirmed on PDE-EVs. At the same time, the absence of CD11b (monocyte, granulocyte marker) and CD34 (hematopoietic progenitor cells, marker of endothelial cells) was confirmed. Our data suggest that the sources of PDE-EVs may be mesothelial cells, had previously undergone mesenchymal dedifferentiation/transition and detached from the mesothelial layer into PDE. EV treatment increased the mRNA expression of interleukin (IL)-10 and monocyte chemoattractant protein-(MCP)-1 of PBMCs. Moreover, the expression of these factors became even more pronounced after their induction with lipopolysaccharide. Phytohemagglutinin induced production of tumor necrosis factor (TNF)-α or IL-6 of PBMCs was not affected by EV treatment.

Conclusion: Based on our results PDE derived EVs have mesothelial origin and may affect the cytokines balance, they can moderate the "excessive" activation of the immune system and promote tissue regeneration.

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PI-11

The role of urodynamics detecting neuropathic bladder dysfunction in non-urological diseases

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Background: Uroflowmetry is a non-invasive, quick and easy-to-use urodynamic diagnostic tool in the evaluation of voiding function. In bladder dysfunction caused by impaired detrusor muscle contraction (e.g. in autonomic neuropathy), both maximal urine flow (Q_{max}) and acceleration of the detrusor muscle contraction (Q_{acc}) decrease.

Aims: To assess the use of urodynamics in non-urological diseases.

Methods: First, a single-arm meta-analysis was performed and positive event rates were pooled for statistical analysis to assess the urodynamic parameters of diabetic women. The study was in line with the protocol registered in PROSPERO (CRD42021256275).

Then, a single-centre, retrospective cohort study was conducted with 270 healthy children between 6 and 18 years to determine Q_{acc} parameters by voided volumes. Quantile method was used to establish the 3–97th percentile levels of Q_{acc} with SPSS. The centile curves of acceleration by voided volume were estimated by using lmsChartMaker Pro 2.3 software based on the LMS method.

Results: Out of 1750 records (MEDLINE, n = 454; Embase, n = 773; CENTRAL, n = 63; and Web of Science, n = 460), a total of 140 articles were assessed for eligibility by full text, of which 10 studies were used in the quantitative synthesis, that reported on a total of 2342 diabetic patients. The mean Q_{max} (n = 1620) is 18.80 mL/sec [95% CI: 15.27–22.33] with a considerable level of heterogeneity (I^2 = 99%). The mean maximal detrusor pressure at Q_{max} (n = 1211) is 30.13 cmH_2O [95% CI: 25.53–34.73],(I^2 = 90%). The mean first sensation of bladder filling (n = 1201) is 178.66 mL [95% CI:150.59–206.72],(I^2 = 97%). The mean maximal cystometric capacity (n = 1178) is 480.41 mL [95% CI:409.32–551.50],(I^2 = 98%).

Out of 270 healthy children, 208 were enrolled in the analysis who performed 404 micturition total. We found an inversely proportional correlation between voided volumes and Q_{acc} parameters.

Conclusion: Diabetes is an important independent risk factor for lower urinary tract symptoms. As urodynamics can detect early alterations in voiding function, it might help to apply interventions to delay or prevent the onset of diabetes to limit difficulties in voiding.

We have established nomograms for normative reference values of Q_{acc} in paediatric population (girls and boys separately) by voided volumes in centile forms.

PI-12

Urinary albumin excretion in healthy Hungarian children

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Introduction: Although microalbuminuria is known as an independent predictive and prognostic marker of cardiovascular morbidity and mortality, there are only few studies about the incidence and reference range of urinary albumin excretion in childhood.

Aim of the study: to investigate the difference of urinary albumin excretion between healthy children with normal weight and overweight/obesity (OW/O). Furthermore our aim was to evaluate urinary albumin/creatinine ratio (U-ACR) in relation to the chidren's age and gender.

Study participants and methods: Children were recruited from elementary and secondary schools from three towns (Nagykanizsa, Pécs, Zalaegerszeg) in Hungary. The study design was approved by the National Medical Research Council (ETT TUKEB 4536-2/2012/EKU).

Altogether n=805 children (n=419 boys) aged 3 to 16.8 years were participated to collect random morning urine samples. Among these children n=183 (22.7 %) were overweight or obese. Urinary albumin concentration was determined by immunoturbidimetry and urinary creainine concentration (Jaffe method) was also measured and used U-ACR to compensate for the variations in the concentration of random urine samples. Statistical analysis was performed using non-parametric (Wilcoxon signed-rank) test.

Results: U-ACR was significantly higher in children with normal weight compared to children with OW/O (12.02±33.46 vs 11.52±38.56 mg/g, p=0.036). This difference was present only among girls (14.38±28.98 vs 10.17±21.34 mg/g, p=0.025), but not in boys. U-ACR was significantly higher in normal weight girls than in normal weight boys (girls: 14.38±28.98 vs boys: 9.92±36.89 mg/g, p=0.004), while this difference between sexes was not present in the OW/O group. Three different groups were created by ages (1. childrens <10 years, 2. childrens 10-<12 years, 3. childrens >12 years old). In the 2nd group there was also a significant difference between the two sexes among children with normal weight (girls: 15.31±27.2 vs boys: 6.55±5.79 mg/g, p=0.022).

Conclusions: a significant difference of U-ACR was found between normal weight and OW/O children. In accordance with the literature our results confirm that U-ACR are significantly higher in girls which can be explained by the lower muscle mass and urinary creatinine excretion of them. No relationship could be determined between U-ACR and different age groups. These are preliminary resulst, and further investigations are needed especially to establish age- and sex-specific reference values for urinary albumin excretion in healthy children.

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PI-13

Nephroblastoma in children: A single-center experience

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Background: Nephroblastoma or Wilms tumor (WT) is the most common renal tumor in children, with a peak incidence at the age of 3. WT usually manifests as an asymptomatic palpable abdominal mass. Histological diagnosis and staging are the two most significant prognostic indicators. Treatment is usually a combination of surgery, chemotherapy and radiotherapy, with 5-year survival rate of nearly 90%.

Aim: The aim of this study was to analyze clinical presentation, diagnostic evaluation, treatment, and outcome in children with WT during a 10-year period.

Methods: The retrospective study included 7 children (4 girls, 3 boys) diagnosed with WT at the Department of Pediatrics, Clinical Hospital Center Rijeka, from January 1, 2013. to December 31, 2022.

Results: The mean age of patients was 3.5 (1.1–8.3) years (the median age is 3.1). Three (42%) patients presented with a palpable mass in the abdomen. Two (28.6%) patients had hematuria. One (14%) patient had hemihypertrophy. The median time from sign/symptom onset to seeking professional help was 4 (0–10) days, and to diagnosis 10 (3-54) days. The diagnosis was established by ultrasound-guided fine needle biopsy in all patients. The treatment was conducted according to SIOP protocols. All patients received preoperative chemotherapy: six (86%) patients VA (vincristine/actinomycin) and one (14%) patient received VAD (vincristine/ actinomycin/doxorubicin). Radical nephrectomy was performed in all patients, with lymphadenectomy in five (71,4%) of them. Histologically, all patients had a mixed type of tumor (intermediate risk group). Four (57%) patients had stage I, one (14%) stage II, one (14%) stage III, and one (14%) patient with lung metastases had stage IV. Postoperative chemotherapy was performed in all patients: five (71%) of them received VA, and two (29%) received VAD. In three (42.8%) patients the staging was revised during postoperative treatment: two patients were upstaged after central histological review, and one was understaged after lung biopsy that excluded metastases. No patient received radiotherapy. The most common side effect of chemotherapy was vincristine polyneuropathy, presented in all patients, followed by myelosuppression in patient with VAD chemotherapy. All patients are in complete remission, with the median follow up of 7.1 years (2.1 – 9.5).

Conclusion: Children with WT are successfully treated in our institution, but some limitations are noticed. Due to its rare occurrence in a small oncology center, participation in large clinical trials and collaboration with experienced multidisciplinary team are of utmost importance in the future care for children with WT.

PI-14

ABPM validation in childhood

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Background: Nowadays even paediatrics is experiencing the increasing number of high blood pressure cases. For the sufficient diagnosis, for defining the optimal therapy, for identifying potential target organ failures and for the follow up the 24 hour long blood pressure monitoring with ABPM (ambulatory blood pressure monitoring) equipment is inevitable. Out of the 31 available devices only two are validated for the paediatric population.

Aims: Our aim was to gain reliable information about the accuracy of the Meditech ltd. ABPM-06 machine. If our results meet the criteria of the validation, we could provide a new device for the clinical use.

Methods: For the validation process initially we used the protocol of the British Hypertension Society, in which we included 55 children aged between 5 and 15 years.

After completing phase IV – static device validation - the differences between the test instrument and the mercury sphygmomanometer were calculated separately for each observer and separately for systolic (SBP) and diastolic blood pressure (DBP).

Results: After grouping the differences between the mercury sphygmomanometer and the tested machine, we found that 46% was within 5 Hgmm and 82% was within 10 Hgmm considering the systolic measurements; for the diastolic 52% was within 5 Hgmm and 82% within 10 Hgmm.

Conclusion: Although the first results showed that this machine is not sufficient for the clinical use according to this study, our final conclusion was that due to the lack of suitable protocol and the small number of participants we cannot make unwarranted assumptions. Therefore we are currently performing an extended study in accordance with the protocol of the International Organisation of Standardization.

PI-15

Anaplastic ependymoma – a rare cause of hypertensive hydrocephalus in an infant

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Keywords: anaplastic ependymoma, hypertensive hydrocephalus

Anaplastic ependymoma is a highly aggressive tumor that can cause life threatening complications. The aim of the case presentation is to raise awareness of the existence of rare neoplasms with symptoms of increased intracranial pressure and brain herniation. Early suspicion, appropriate diagnosis and treatment can result in a complete cure.

A four-month-old girl was referred to Clinical Hospital Center Rijeka by a primary care physician due to an increase in head circumference, irritability, and high-pitched cry. Physical examination revealed hypertonus, downward gaze ("setting-sun" sign), swollen veins over the scalp, bulging fontanelles and separated sutures. Brain ultrasound showed large hydrocephalus with left-sided supratentorial formation. Computed tomography demonstrated expansive formation of the left hemisphere with hypertensive hydrocephalus. Magnetic resonance imaging verified left supratentorial tumor measuring 100x62x74 mm (APxLLxCC). Dilated left lateral ventricle and the third ventricle were pushed to the right side, with subfalcine herniation of 11 mm. The patient was transferred the same day to the Clinical Hospital Center Zagreb for emergency neurosurgical intervention. Complete tumor resection was performed. Histopathological diagnosis was anaplastic ependymoma grade III. Postoperative course was uneventful. After recovery, the patient was transferred to our hospital for further treatment. Adjuvant chemotherapy according to the HIT 2000 protocol was carried out, without serious toxicity. Eight years after the end of the treatment, the girl is in continuous remission and regular physical growth and intellectual development.

Anaplastic ependymoma is a rare pediatric tumor of uncertain prognosis. The mainstay of the treatment remains maximal safe surgery (ideally gross surgical resection), followed by adjuvant chemotherapy. Recent genetic studies have led to the identification of biologically distinct subtypes, suggesting more adequate means for risk stratification. Early diagnosis and appropriate treatment contribute to a successful outcome.

PI-16

Upper mediastinal syndrome caused by non-Hodgkin lymphoma: A case report

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Keywords: children; emergencies; mediastinal tumor; superior vena cava syndrome

Aim: To present the case of a pediatric patient with superior mediastinal syndrome (SMS) in whom a preliminary diagnosis of T-cell non-Hodgkin lymphoma (T-NHL) was established by cytological analysis of pleural and pericardial effusion and due to the life-threatening condition, chemotherapy was initiated with an excellent response. Case report: A 15-year-old girl was examined in the emergency pediatric department due to unspecified loss of consciousness. Five days before the admission, she was complaining of tinnitus, dizziness, night sweats, diffuse abdominal pain and vomiting, and dry cough on the day of the admission. Her clinical condition worsened rapidly with cyanosis and hypoxia, and she was admitted to the Intensive Care Unit. Imaging studies demonstrated a mediastinal mass, and large pericardial and pleural effusion. Along with intensive supportive measures, pericardiocentesis and pleural drainage were performed. Cytological examination of fluids established a preliminary diagnosis of T-NHL, and chemotherapy according to EURO-LB 02 protocol was started without histological confirmation, with excellent response. Five years after the end of the treatment, the patient is in complete remission. Conclusion: SMS is an emergency in pediatric oncology. The rapid development of typical SMS signs and symptoms in a child should arouse clinical suspicion of a mediastinal tumor. In life-threatening cases, along with intensive care treatment, it is necessary to start anticancer therapy based on a preliminary diagnosis without histological confirmation. Early identification and adequate treatment of SMS are crucial for a favorable outcome.

PII-01

The association of hypertension with vitamin D deficiency and serotonin dysregulation in obese children

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Background: Obesity and hypertension represent a significant health challenge affecting the pediatric population with increasing prevalence. Vitamin D deficiency has been suggested to be associated with arterial hypertension. Due to disruption of the signaling pathways activated by the vitamin D receptor, there is increased vascular stiffness, which results in impaired systolic and diastolic heart function increase from renin-angiotensin system activity. Recently, the biological mechanism by which vitamin D regulates serotonin synthesis has been described. Through different receptors serotonin either directly or indirectly by modulating nitric oxide synthase affect blood pressure regulation.

Aim: The aim of this work was to investigate the relationship between vitamin D and serotonin in association to blood pressure in obese children.

Methods: One hundred and seventy-one children were enrolled in the prospective cross-sectional study. Children were divided into two groups according to body mass index status, a group of children with obesity (BMI ≥95th percentile; *n*=120) and non-obese children (*n*=51). All children in the obese group were obese for more than four years, the had no history of underlying diseases or family history of diabetes, they did not get any therapy for weight control or did not get any vitamin D supplementation in the past year. All children underwent office and ambulatory blood pressure monitoring and biochemical analysis of vitamin D and serotonin. Data on fasting glucose, insulin, HOMA, uric acid, and complete lipid profile were obtained in obese children.

Results: Hypertension was found only in the group of obese children. Compared to the control group, children with obesity had lower concentrations of both vitamin D and serotonin, especially in winter. The vitamin D seasonality and BMI-SDS were shown as the most significant predictors of the changes in systolic blood pressure, while diastolic blood pressure was predicted mostly by insulin and serotonin. The presence of hypertension and high-normal blood pressure in obese children was most significantly affected by hypovitaminosis D and increased BMI-SDS. The vitamin D seasonality significantly correlated with decreased serotonin.

Conclusions: These results suggest that dysregulation of the followed metabolic hormones can pose a risk of the onset and development of hypertension in children with obesity; therefore, their optimization altogether with body weight reduction may improve the long-term cardiovascular health of these children.

PII-02

Correlations of cardiometabolic parameters with pulse-wave velocity in normal and obese children

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Aim of the study: We aimed to compare some laboratory and anthropometric characteristics of normal weight and obese children in correlation to pulse-wave velocity (PWV) values. Our primary interest was to evaluate, using multivariate regression, which parameters mostly correlate to PWV and help us to elaborate risk factors for development of cardiovascular disease.

Patients and methods: Prospective cross-sectional study of 64 overweight and normal weight children was performed at the University Medical Centre Maribor, Department of Paediatrics. Data from lean healthy controls without arterial hypertension were gathered in October 2022 and data from patients from November 2022 to March 2023. We obtained anthropometric measurements, metabolic laboratory values, body composition indices, as well as carotid and radial PWV values. Active antihypertensive or other chronic disease therapies were deemed as exclusion criteria.

Results: 38 overweight and obese children (20 male), with or without arterial hypertension, median age 14 years, and 26 lean healthy controls (12 male), median age 14 years, participated in the study. Median BMI z-scores were 2.1 and 0.24 in the patient and control groups, respectively. Single-measurement systolic ($p<0.001$) and diastolic blood pressure (BP) ($p=0.001$), alanine aminotransferase ($p<0.001$), gamma-glutamyl transferase ($p<0.001$), uric acid ($p<0.001$), high-density lipoprotein ($p=0.08$), apolipoprotein B ($p=0.018$) and vitamin D ($p=0.012$) values differed between patient and control groups using nonparametric tests. In a combined group multivariate regression model serum creatinine, apolipoprotein A, waist and hip circumference were significant predictors of PWV, obtaining a R^2 value of 0.28. Interestingly, only extracellular water content was significant predictor of PWV using multivariate analysis in the patient-only and combined group analysis.

Conclusions: Our study confirmed usefulness of PWV in obesity diagnostics. Using a multivariate regression model, a significant correlation between apolipoprotein A, creatinine, waist, and hip circumference and PWV values was shown in both groups, which further exemplifies the importance of these biomarkers as cardiovascular risk factors in the pediatric population. Extracellular water content was the only significant body composition marker.

PII-03

Analysis of body mass index of infants and children in northern Hungary

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Background: Childhood obesity is a serial health crisis that is expected to lead to a dramatic rise in the incidence of obesity-associated morbidities in the next decade. Clinical assessment of anthropometric data is key for early diagnosis and intervention.

Aims: The aim of our research is to refine indicators of pre-obesity and obesity among pediatric patients. We intended to collect and analyze anthropometric data of children in the Northern Hungarian region. We calculated the distribution of body mass index (BMI), and BMI-SDS (BMI standard deviation score) values at each age group and in the two genders, and compared these values to the national average.

Methods: We collected anthropometric data from the clinical archive of our children's hospital, arranged them according to age and gender, and compared the obtained data with the values included in the current guidelines on obesity / adiposity status assessment.

Results and conclusion: In the 12-year-old age group, the variance and the standard deviation of BMI values clearly increased in both sexes, that can be explained by adipose tissue remodeling in puberty. In addition, we noticed that the average BMI of each age group was reaching the overweight category. Based on our data the average BMI of all age groups were considered stage 1 overweight.

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PII-04

Comparison of sonographic measures of central adiposity with some anthropometric and biochemical parameters in lean and obese children

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Aim of the study: We aimed to compare some laboratory and anthropometric characteristics of paediatric overweight and obese patients to healthy lean controls with sonographic measurements of visceral and abdominal fat thickness.

Patients and methods: Prospective cross-sectional study of 64 overweight and normal weight patients examined at the Department of Paediatrics, University Medical Centre Maribor. All participants were screened for confounding factors, including regular therapy and comorbid states, which may influence cardiometabolic health indices. Data from lean healthy controls were gathered in October 2022 and patient data from November 2022 to March 2023. Clinical, laboratory and abdominal ultrasound data were analysed.

Results: We recruited 38 overweight and obese children (20 male), with or without arterial hypertension, median age 14 years, and 26 lean healthy controls (12 male), median age 14 years. Median BMI z-scores were 2.1 and 0.24 in the patient and control groups, respectively. We observed greater visceral (median 58 cm) and subcutaneous (median 35 cm) fat thicknesses in the patients as compared to the control group ($p < 0.001$). Greater visceral fat was seen in females and was positively correlated with systolic and diastolic blood pressure (BP), glycated haemoglobin HbA1c, thyroid stimulating hormone (TSH), haemoglobin, alanine aminotransferase (ALT) and gamma-glutamyl transferase (γGT), uric acid, high-density lipoprotein, apolipoprotein B and negatively to vitamin D values. Multivariate linear regression of visceral fat thickness yielded an R^2 value of 0.52 using ALT, uric acid, fasting glucose, TSH and vitamin D levels. Similarly, subcutaneous fat thickness was correlated with γGT, diastolic BP, ALT, cystatin C and homocysteine values in a multivariate model.

Conclusions: Our results show a significant correlation between visceral fat thickness and ALT, uric acid, fasting glucose, vitamin D and TSH levels in a population of lean and obese children and adolescents and usefulness of ultrasound in obesity diagnostics.

PII-05

Can vascular consequences of obesity be measured in children? – Technical feasibility study of Bókay early cardiovascular prevention program

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Background: Epidemiological data shows modifiable risk factors have a decisive role in the development of cardiovascular diseases. Previously, these modifiable risk factors, including obesity, were mostly present in the adult population, however in the last decades they have also become prevalent among children. According to recently published data, one in three school-aged children in the WHO European Region are living with overweigh or obesity. This obesity pandemic will have devastating public health consequences via the accelerated development of cardiovascular diseases in this population.

Aims: Our goal was to investigate if structural and functional vascular changes associated with childhood obesity can be objectively and reproducibly measured decades before the symptoms of any manifest cardiovascular disease.

Methods: We conducted a comprehensive literature review to identify proven and feasible methods to assess the vascular system in obese children. Invasive, risky, time-consuming or costly technique were excluded.

Results: We identified five techniques for further evaluation with available evidence of good prognostic value. Two of these methods, *carotid-femoral pulse wave velocity measurement* and *brachial artery flow mediated dilation measurement* can assess the changes of large-vessel, three of them, *computer assisted analysis of fundus photography*, *dynamic fundus vessel analysis* and *skin capillary flow mediated dilatation measurement* can assess microvascular parameters. Each technique can provide a unique and valuable insight to the structural and functional vascular changes associated obesity. The measurements with these techniques can be repeated several times without any risk to the patient, which makes it possible to perform follow-up investigations on our patients. They are also easy-to-use and reproduceable, which makes them ideal to a large-scale cohort study with multiple groups of patients. Most importantly, no technical or ethical limitation prevent us to use them on children.

Conclusions: We identified five techniques which we can use to assess the vascular consequences of childhood obesity. These measurements will make it possible to assess the efficacy of different cardiovascular prevention strategies in our upcoming Bókay Early Cardiovascular Prevention Program.

PII-06

Clinical characteristics of Polycystic Ovary Syndrome in adolescents

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Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, but during adolescence the diagnosis of it is challenging, because no evidence-based guideline exists.

Aims: to investigate the clinical characteristics of PCOS at the diagnosis and after one year follow-up.

Patients and methods: altogether n=32 adolescent girls (n=6 girls with normal weight) were examined (mean age±SD:14.8±1.6 years; BMI: 32.6±8.2 kg/m2). Antropometric parameters (body weight, height, calculated body mass index /BMI/) were determined, clinical signs of hyperandrogenisms (acne, hirsutism, alopecia) were also identified, laboratory analyses (gonadotrop hormones, androgenes, insulin, blood glucose. lipids) and pelvic ultrasound were performed.

Statistical analysis was performed using parametric (ANOVA) test. Data are reported as mean±SD. The study design was approved by the Regional and Local Research Ethic Committee, University of Pécs.

Patients were followed up for a year. Lifestyle modification recommendations were suggested at the diagnosis, medical therapy was started in the cases without any positive achievements after half year.

Results: Menstrual cycle irregularity was found to be the most common symptom (71.9 %) among girls while prevalence of hirsutism was 46.9 % and acne was only 12.5 %. Ovarian cysts were detected in 75 % of the patients. According to the BMI significant differences were found in fasting glucose (5.0±0.4 mmol/l vs 4.6±0.2 mmol/l, $p<0.05$) and prandial Se insulin (221.3±167.5 pmol vs 55.2±20.7 pmol/l, $p<0.05$) levels between adolescents with overweight or obesity (OW/O) and with normal weight. However no differences could be detected between the two groups in the hormonal status (LH/FSH ratio, androgen levels, sex hormone binding globulin /SHBG/, Se prolactin). In all patients with OW/O lifestyle changes were recommended. After half year the mean BMI was decreased (35.2±6.7 vs 33.1±7.1 kg/m2), but it was not a significant change and some clinical signs were improved, so almost half of the girls with OW/O (42 %) medical therapy was needed.

Conclusions: In accordance with the literature obesity was a common comorbidity in adolescent girls with PCOS in our study and we could also confirm that ovarian cysts could not be detected in all adolescents. Metabolic disorders were more frequent compared to hormonal changes in PCOS in our investigation. Our preliminary results also emphasize the need for prospective studies to provide evidence-based recommendations in clinical practice for specialists to treat PCOS in adolescence.

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PII-07

Admission risk factors and predictors of moderate or severe pediatric acute pancreatitis: A systematic review and meta-analysis

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Background: Pediatric acute pancreatitis (PAP) has an increasing incidence and is now estimated to be almost as common as in adults. 20-30% of PAP patients will have a moderate or severe disease course (M/SPAP), characterized by organ failure, local or systemic complications. There is still no consensus regarding on-admission severity prediction in these patients.

Aims: Our aim was to conduct a systematic review and meta-analysis of available predictive score systems and parameters, and differences between on-admission parameters in mild and M/SPAP.

Methods: We conducted a systematic search on the 14th February, 2022 in MEDLINE, Embase and CENTRAL. We performed random-effects meta-analysis of on-admission differences between mild and M/SPAP in laboratory parameters, etiology, demographic factors, etc. calculating risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI) and created forest plots. For the meta-analysis of predictive score systems, we generated hierarchical summary receiver operating characteristic curves using a bivariate model. Chi-squared tests were performed and I^2 values calculated to assess statistical heterogeneity.

Results: 45 studies – mostly retrospective cohorts – were eligible for inclusion. Among predictive score systems examined by at least 5 studies, the modified Glasgow scale had the highest specificity (91.5% for values ≥3), and the Pediatric Acute Pancreatitis Severity score the highest sensitivity (63.1% for values ≥3). The performance of other proposed score systems and values were summarized. Traumatic (RR: 1.70 95% CI: 1.09-2.67) and drug-induced (RR: 1.33 95% CI: 0.98-1.87) etiologies were associated with a higher rate of M/SPAP, while anatomical (RR: 0.6195% CI: 0.38-0.96) and biliary (RR: 0.72 95% CI: 0.53-0.99) PAP tended to be less severe.

Conclusions: Many predictive score systems were proposed to assess the possibility of M/SPAPcourse. While the most common ones exhibit good specificity, they all have subpar sensitivity. Our systematic review provides a rigorous overview of predictive options assessed thus far, that can serve as a basis for future improvement of scores via the addition of parameters with a better observed sensitivity: e.g. lipase exceeding 7-times the upper threshold, hemoglobin, etc. The addition of etiological factors is another possibility, as they can herald a more severe disease course.

PII-08

Necrotizing fasciitis in childhood

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Background: Necrotizing fasciitis (NF) is a severe soft tissue infection affecting the epidermis, dermis, subcutaneous tissue, fascia, and muscle causing massive tissue destruction with the incidence 0.022 to 0.843 cases per 100.000 children. NF is characterized by rapid progression and the development of a life-threatening condition. It can occur among healthy children as well at any age. Because of a potentially high risk of permanent soft tissue damage and mortality early diagnosis is crucial but often confounded by numerous factors.

Aims and Methods: During the last 5 years 15 NF was diagnosed in our Institute. We introduce one of the most serious case.

Results: A 17-year-old female with swelling, pain and erythema of the left hand was admitted to our Institute on 07.08.2022. One day prior she had an insect sting on the same localization one day prior. Due to tachycardia and low blood pressure on admission, she was initially mistreated as a severe allergic reaction (anaphylaxis). Laboratory parameters showed elevated inflammatory reaction. Examination of the dorsal area of the left hand revealed swelling and edema with pallor on the fingertips. At the center of the insect bite a pinhead size of a bluish area was seen with one pinhead size of a bulla. Broad spectrum antibiotics (ceftriaxone) was initially started, but sepsis progressed since tachycardia and hypotension persisted. On the second day of hospital stay imaging diagnostics (ultrasound and MRI) were taken which revealed the signs of NF. High dose penicillin and clindamycin were started and surgical debridement of all necrotic tissues was done. Blood cultures as well as swab culture grew Streptococcus pyogenes. After 4 days of antibiotic treatment and surgical intervention, general condition and symptoms showed rapid improvement. She received antibiotic treatment for a total of 10 days.

Conclusion: As NF is a potentially life-threatening soft-tissue infection, prompt diagnosis and treatment is crucial. Unfortunately it is often associated with delayed suspicion and surgical debridement which amplifies the severity of the disease and poor outcome. In a patient with a defined entry point for bacteria, physical examination is of significant importance for pain, swelling and erythema of the affected area. Laboratory signs are helpful, but continuous re-evaluation of physical examination findings, including vital signs are the most important factors in the approach to the patient with a soft tissue infection. Surgical intervention is the most important factor for control of the bacterial infection, as antibiotic treatment alone does not bring full resolution.

PII-12

Age-specific prevaccination CD3+CD56+ (NKT-like) cells and the outcome of influenza vaccination in children undergoing chemotherapy

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Background: Seasonal prevention of influenza infections is paramount in the management of pediatric patients with malignancies. However, this population is less likely to mount a sufficient immune response compared to healthy children.

Aims: In our study we investigated the effect of CD3+CD56+ natural killer T-cell (NKT)-like cells on the antibody response elicited by inactivated influenza vaccines.

Methods: We enrolled 25 children (aged between 2-18 years) receiving cytostatic treatment for different types of malignancies. Trivalent, inactivated, adjuvanted influenza vaccines were administered to our patients in two consecutive seasons. Blood samples for flow cytometry and serological analyses were collected before and 21-28 days after the vaccination. Serological response was determined by measuring hemagglutination inhibition titers. By flow cytometry, we examined the total numbers and percentages of CD3+, CD4+, CD8+ T cells, naive (CD3+CD45RA+) and memory (CD3+CD45RO+) T cells and CD3+CD56+ (NKT-like) cells. Lymphocyte subpopulation results were compared to age-related reference values and their relationship to specific antibody responses (seroprotection, seroconversion, geometric mean titer (GMT), geometric mean fold increase (GMFI)) was evaluated using one-way ANOVA and the paired sample t test.

Results: Patients with prevaccination CD3+CD56+ (NKT-like) cells above age-specific predicted values showed significant associations both in postvaccination GMT elevation (H1N1: 75.11 vs. 14.14, p=0.010; H3N2: 62.18 vs. 11.22, p=0.012; B: 22.69 vs. 6.67, p=0.043) and GMFI against all three strains (H1N1: 3.76-fold vs. 1.06-fold, p=0.015; H3N2: 2.74-fold vs. 1, p=0.013; B: 2.57-fold vs. 1, p=0.008).

Conclusions: Our results suggest an association between NKT-like cell counts and the specific antibody response against all three investigated influenza strains in highly immunosuppressed patients.

PII-13

Challenges and novel therapeutic approaches in pediatric non-Hodgkin lymphoma

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Introduction: Non-Hodgkin lymphoma (NHL) is the fourth most common malignancy amongst children with lymphoblastic lymphoma (LBL), diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma (BL) and anaplastic large cell lymphoma (ALCL) as the four major subtypes. Despite the excellent 5-year overall survival rate of above 90%, novel agents of targeted treatment are required, especially in relapsed and refractory cases.

Aims: Our aim was the retrospective analysis of recent differential diagnostic and therapeutic experiences in pediatric NHL cases, with an emphasis on novel treatment opportunities.

Methods: During the previous three years, 6 patients have been newly diagnosed with NHL in our clinical centre, representing all common subtypes of pediatric NHL (n=3 LBL, n=1 DLBCL, n=1 BL and n=1 ALCL). Initial diagnostic work-up included histopathological and molecular analysis, immunohistochemistry and PET-CT scan in all patients. Detailed clinical evaluation of cases involved demographic data, treatment responses and occurrence of serious complications as well.

Results: In case of our three patients with T-LBL, major presentational signs included the development of a bulky abdominal tumour following the resection of a thymoma, combined cervical plus axillary lymphadenopathy, and mediastinal involvement in the third case. Treatments were performed according to the LBL 2018 Protocol. The patient with DLBCL showed cervical lymph node swelling, the histological examination of which revealed the transformation of follicular lymphoma into DLBCL. Treatment was started according to the Inter-B-NHL 2010 Protocol. Rapid progression of abdominal pain and ascites with an extremely elevated LDH value were the initial findings in the patient with BL. Treatment according to the Inter-B NHL ritux 2010 Protocol was completed with the administration of rituximab. Earliest symptom of patient with ALCL was axillary lymphadenopathy. Biopsy sample of the lymph node was confirmed to be positive for CD30 and ALK stainings. Despite the immediate initiation of therapy according to the ALCL99 Protocol, patient has relapsed within 1 year from the time of the diagnosis. Based on literature data, further chemotherapy was supplemented with brentuximab-vedotin. At present, five of the 6 patients are in good general condition with Karnofsky Grades of 90-100. Major complications during treatment include pancreatitis, tumor lysis syndrome and acute respiratory distress syndrome.

Conclusions: Our experiences reflected international trends, including novel treatment opportunities in pediatric NHL. However, excellent treatment results could be further improved in the future via the administration of novel agents of personalized therapy, careful differential diagnostic evaluation and close observation of physical status are nevertheless of distinguished clinical significance.

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Retrospective analysis of clinical data in acute lymphoblastic leukemia (2000-2019) in comparison with GEO gene expression results of epigenetic modifiers

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Background: Acute leukemias account for nearly one-third of pediatric malignant diseases, among which acute lymphoblastic leukemia (ALL) accounts for three-quarters.

Aims: Our aims were to retrospectively analyze the clinical data of n=141 patients diagnosed with ALL between 2000 and 2019 at the Division of Pediatric Hematology-Oncology in Debrecen and to compare the results with the published data from the field and the corresponding repositories of the GEO gene expression database.

Methods: Data collection was carried out with the archive version of the e-MedSolution program and paper-based documentation. Statistical analysis was performed using Graphpad Prism 8.0.1. programme.

Results: Average age of the patients (54% boys, 46% girls) was 6.2 years at the time of the diagnosis. B-cell precursor ALL and T-ALL was registered in 82.3% (n=116) and 16.3% (n=23) of cases, respectively. At the time of diagnosis, 74.5% of average blast percentage was detected in the bone marrow. Anaemia (89.4%, n=126) and thrombocytopenia (84.4%, n=119) were the most frequent abnormalities in initial blood counts. In the majority of patients (83%, n=117), central nervous system involvement has not been confirmed. On day 8, 83.7% (n=118) of patients had a good prednisolone response (PGR), while 9.9% (n=14) gave a poor response (PPR). PGR and PPR were statistically significantly more common among patients with t(12;21) ($p<0.05$) and t(9;22) ($p<0.0001$) translocations, respectively. On day 33, 81.6% (n=115) were in complete remission. Allogeneic bone marrow transplantation was performed in 11.3% (n=16). Ratio of relapsed patients was registered as 17% (n=24).

Most common genetic abnormalities were hyperdiploid karyotype (26.2%, n=37), supranumerary chromosome 21 (23.4%, n=33), t(12;21) translocation (22.7%, n=32), extra chromosome X (16.3%), n=23), TELdel mutation (9.2%, n=13) and MLL1 gene rearrangement (7.1%, n=10). In case of MLL1 involvement, relapse rate was significantly higher ($p=0.022$).

According to GEO database, expression of KDM5D ($p<0.0001$) and Ago4 ($p<0.0001$) were significantly higher, while the expression of HDAC9 was significantly lower ($p<0.0001$) in case of t(12;21) translocation. In the subgroup of patients with late relapse, expression of KDM5B ($p=0.017$) and INO80 ($p=0.004$) genes were significantly higher, while the expression of PGAM1 was significantly lower ($p<0.0001$) compared to non-relapsed patients.

Discussion: Based on retrospective data analysis, better therapeutic response was observed in case of favorable genetic variations. According to data in GEO database, different genetic variations are associated with distinct epigenetic and proteomic profiles, based on which detailed evaluation of these alterations may contribute to the identification of new biomarkers, therapeutic targets.