

Selected Lectures of the 15th International Workshop on Neonatology and the 40th Congress UMEMPS (Union of Middle-Eastern and Mediterranean Pediatric Societies)

CHILDREN OF THE MIDDLE-EASTERN AND MEDITERRANEAN AREA: WE CAN DO BETTER!

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LECT 1

THE FUTURE OF PREMATUREITY

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Worldwide, 15 million babies are born preterm each year, about 11% of all deliveries. Prematurity carries a high global health burden because of its implications for mortality and acute and chronic morbidity. Advances in perinatal care allowed survival of extremely preterm infants, and follow-up studies are now uncovering the long-term outcomes in adulthood. Sequelae of preterm birth include respiratory, neurodevelopmental, cardiovascular, metabolic, and growth disorders.

Although a decreased incidence of several prematurity-related morbidities (necrotizing enterocolitis, sepsis, brain lesions, retinopathy) was reported in the past two decades, bronchopulmonary dysplasia (BPD) still represents a relatively common chronic morbidity affecting about 50% of infants born at 25 weeks of gestational age (Vermont Oxford Network), and can impact respiratory health in adult life. Its long-term outcomes are highly variable based on the different phenotypes (alveolar, obstructive, vascular) and the interactions with genetic, epigenetic, and gender influences. Furthermore, respiratory diseases in individuals born preterm also include non-BPD phenotypes, such as airway malacia, obstructive sleep apnea, and control of breathing issues.

Importantly, prematurity is associated with long-term neurodevelopmental impairments, with the youngest infants bearing the highest risk. Besides major disabilities (cerebral palsy, intellectual disability, blindness and deafness) affecting up to 15% of very preterm infants and mainly associated to the occurrence of severe brain lesions, almost 25-50% of these babies manifest, later in

childhood and adolescence, minor to moderate neurodevelopmental disorders, including learning and behavioral problems, even in absence of overt brain damage at conventional neuroimaging. Pathogenesis of “encephalopathy of prematurity” is complex: impaired brain growth and maturational disturbances have been proposed as underlying mechanisms and attributed to perinatal risk factors and severity of postnatal morbidities. However, more recently, early exposure to adverse postnatal life events has been reported to impact the developmental trajectories of preterm children via epigenetic alterations of imprinted and stress-related genes.

Finally, prematurely born infants are more likely to develop high blood pressure and glucose intolerance from childhood, increasing the risk for future chronic cardiovascular and metabolic diseases. The causes include impaired vasculogenesis and organogenesis as well as postnatal nutrition, growth and possible epigenetic modifications.

To be noted, unfavorable long-term outcomes also affect late preterm infants, especially with regard to the higher risk of growth faltering and neurodevelopmental impairments compared to term infants.

In this context, preventive strategies and individualized care should be provided from fetal life to childhood to improve the future of our smallest neonates and their families.

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LECT 2

NEONATAL ARTERIAL ISCHEMIC STROKE: REVIEW OF THE CURRENT GUIDELINES

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Neonatal arterial ischemic stroke (NAIS) is a rare event that occurs in approximately one in 5,000

term or close-to-term infants. Most affected infants will present with seizures. Although it is a well-recognized clinical entity, many questions remain regarding diagnosis, risk factors, treatment, and follow-up modalities. In the absence of a known pathophysiological mechanism and lack of evidence-based guidelines, only supportive care is currently provided. To address these issues, a French national committee set up by the French Neonatal Society and the national referral center for arterial ischemic stroke in children drew up guidelines based on a HAS (French national authority for health) methodology. The main findings and recommendations established by the study group are: (1) among the risk factors, male sex, primiparity, cesarean section, perinatal hypoxia, and fetal/neonatal infection (mainly bacterial meningitis) seem to be the most frequent. As for guidelines, the study group recommends the following: (2) the transfer of neonates with suspected NAIS to a Neonatal Intensive Care Unit with available equipment to establish a reliable diagnosis with MRI imaging and neurophysiological monitoring, preferably by continuous video EEG; (3) acute treatment of suspected infection or other life-threatening processes should be addressed immediately by the primary medical team. Persistent seizures should be treated with a loading dose of phenobarbital 20 mg/kg IV; (4) MRI of the brain is considered optimal for the diagnosis of NAIS. Diffusion-weighted imaging with apparent diffusion coefficient is considered the most sensitive measure for identifying infarct in the neonatal brain. The location and extent of the lesions are best assessed between 2 and 4 days after the onset of stroke; (5) routine testing for thrombophilia (AT, PC PS deficiency, FV Leiden or FII20210A) or for detecting other biological risk factors such as antiphospholipid antibodies, high FVIII, homocysteinemia, the Lp(a) test, the MTHFR thermolabile variant should not be considered in neonates with NAIS. Testing for FV Leiden can be performed only in case of a documented family history of venous thromboembolic disease. Testing neonates for the presence of antiphospholipid antibodies should be considered only in case of clinical events arguing in favor of antiphospholipid syndrome in the mother; (6) unlike childhood arterial ischemic stroke, NAIS has a low 5-year recurrence rate (approximately 1%), except in those children with congenital heart disease or multiple genetic thrombophilia. Therefore, initiation of anticoagulation or antithrombotic agents, including heparin products, is not recommended in the newborn

without identifiable risk factors; (7) the study group recommends that in case of delayed motor milestones or early handedness, multidisciplinary rehabilitation is recommended as early as possible. Newborns should have physical therapy evaluation and ongoing outpatient follow-up. Given the risk of later-onset cognitive, language, and behavioral disabilities, neuropsychological testing in preschool and at school age is highly recommended.

LECT 3

CEREBRAL WHITE MATTER: A COMMON DENOMINATOR OF PRETERM BABIES

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The protection of the brain of premature babies represents one of the major challenges of modern neonatology. Many different lesions may develop, some with an incidence inversely related to gestational age (Germinal Matrix Haemorrhage-Intraventricular Haemorrhage [GMH-IVH] and/or Cerebellar Haemorrhage [CBH]) and others with a specific gestational age vulnerability like direct lesions affecting white matter (Periventricular Leucomalacia [PVL] and Periventricular Punctate White Matter Lesions [PVWM]). With the advent of brain ultrasound, we firstly learned to identify and classify major brain lesions while with the progressive improvement of sophisticated MR techniques (i.e. Diffusion Tensor Imaging [DTI]) we are able to diagnose minor lesions (i.e. PVWM) and their effects in impairing the normal development of white matter (WM) structure and microstructure. In addition, the WM microstructure is surprisingly affected not only by minor forms of GMH-IVH as we recently demonstrated (and with a different microstructural pattern according to the changing gestational age suggesting a different pathogenetic mechanism) but also by prematurity “*per se*”, in the absence of detectable brain lesions. Neonatologists are more prone to recognize and accept the idea of a direct insult to WM when they observe the loss of tissue – like during the unilateral venous infarct accompanying the most severe forms of GMH-IVH or with the progressive post-hemorrhagic ventricular dilatation with the resulting WM atrophy. It remains more difficult to ascertain, especially on a clinical basis, that merely a relative postnatal hyperoxia compared

to intrauterine life or an insidious phenomenon like oxidative stress may cause reduced integrity of WM microstructure. Many different mechanisms are involved in the WM specific vulnerability during prematurity, but a further “common denominator” at a microscopic level is, undoubtedly, the developing oligodendrocyte (OL) representing the principal cellular target of the developing WM. Many factors can cause toxicity to the OL precursors, although the role oxidative stress appears to be very common in preterm babies receiving intensive care. Accordingly, proinflammatory cytokines produced in response to hypoxia and infection can become toxic to the pre-OL as well as glutamate excitotoxicity and free radical injury have recently been implicated in pre-OL death. Free iron, in turn causing oxidative stress, contributes to the onset of the OL dysmaturation and it can reduce the expression of differentiation-promoting genes (such as Olig1, Olig2, and Sox10) and increase the expression of differentiation inhibiting genes resulting in an impaired or interrupted OL maturation. In this view, the abnormal WM maturation we can observe with DTI techniques can represent a common denominator of different conditions ranging from minor brain lesions to the less visualizable hazards to OL mediated by different processes like oxidative stress.

LECT 4

EUROPEAN FOUNDATION FOR THE CARE OF NEWBORN INFANTS – PAST, PRESENT, FUTURE

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INTRODUCTION

Worldwide, preterm birth is the leading cause of death during infancy and a major cause of morbidity in both developed and developing countries. Although significant advances have been made in recent years and survival after preterm birth in Europe is high, preterm birth remains a major health issue. A significant proportion of children and their families must cope with long-term physical, psychological, emotional, and financial challenges. The treatment for preterm and ill babies is very complex and requires specially trained healthcare

professionals. Against this background, it is even more worrying that the organization of care, the education of healthcare professionals, and the structure and provision of neonatal care vary widely across Europe.

MATERIALS AND METHODS

The European Foundation for the Care of Newborn Infants (EFCNI) is bringing together parents, healthcare experts from different disciplines, and scientists with the common goal of reducing preterm birth rates and improving the long-term health of preterm and newborn children. Silke Mader, Co-founder, and Chairwoman of EFCNI knows from her own experience that a family needs much more than medical care and support – the entire family needs to be in the center of interest.

RESULTS

Since its establishment in 2008, EFCNI represents the interests of preterm and newborn infants and their families. The foundation is the founder of World Prematurity Day – celebrated each year on 17th November and created in the meanwhile a worldwide network of parent representatives. Just recently, EFCNI founded the GLObal Alliance for Newborn Care (GLANCE). To promote a high and equitable level of perinatal and neonatal care, EFCNI developed, together with 220 experts from over 30 countries, 96 European Standards of Care for Newborn Health. These standards serve as reference standards and need to be translated on a national level. The implementation of the standards will result in more equitable care all around Europe, which will have a long-term impact on preterm and critically ill infants, and their families.

CONCLUSIONS

EFCNI is working on several different projects that all follow EFCNI's vision – to ensure that every baby independent of where it is born receives the best start in life.

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LECT 5

OVERVIEW ON NEONATAL ANEMIA

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INTRODUCTION

Neonatal anemia is defined by hemoglobin and hematocrit concentration below two standard deviations from the mean of postnatal value. It can be a benign or life-threatening condition, because it could present with respiratory distress and, sometimes, neurological alterations. That is why it is important to treat it promptly. In infants reaching the term age, a broad group of causes may contribute to the development of severe anemia, requiring careful clinical investigations in order to obtain an etiological diagnosis.

CAUSES

Possible causes include: 1. Decreased Red Blood Cell (RBC) production due to bone marrow disorders (Blackfan-Diamond anemia, Fanconi anemia, dyserythropoietic anemia), infections (PB19, viral and bacterial sepsis, rubella, HIV), nutritional deficiencies and congenital leukemia; 2. Blood loss due to fetomaternal or twin-to-twin transfusion, which can occur during the delivery, internal bleeding, iatrogenic (excessive blood withdrawals); 3. Increased RBC destruction due to immune reaction (Rh, AB0 or drug-induced), RBC enzyme deficiencies (G6PD, pyruvate kinase), RBC membrane defects (HS, HE, HPP), hemoglobinopathies.

DIAGNOSIS

A careful family, prenatal and perinatal history and a physical investigation associated with peripheral blood smear and a complete blood count are the most important diagnostic tools in the majority of cases. Other important clinical signs are: pale skin, jaundice, hepatosplenomegaly, and skeletal abnormalities. Bone marrow smear and specific genetic tests can be necessary in order to obtain an etiological diagnosis in the presence of rare conditions.

THERAPY

Therapy is targeted at the cause of anemia. Acute blood loss needs transfusion therapy with leucodeplete (cytomegalovirus safe) and eventually irradiated (if the birthweight is less than 1,200 g) blood. The prevalence of neonatal anemia requiring transfusion is relatively high in preterm infants and is often dependent on blood loss due to sampling for laboratory tests and to a suboptimal erythropoietic response. Erythropoietin can be used both in full-term and preterm babies and in hereditary spherocytosis, but in a recent *Cochrane* Review there are no indications for any anemia. Iron therapy is widely used in term, preterm and LWB infants for its role in the erythropoiesis but also in the neurological development; the principal

aim of this therapy is to build hepatic iron stocks. Vitamin E is important as an anti-oxidant element for the RBC membrane, but it is not largely used in clinical practice.

CONCLUSIONS

Neonatal anemia can be a relatively benign condition or the first sign of a wide range of hematological diseases; an etiological diagnosis is critical in order to establish the appropriate treatment.

LECT 6

THE PLACENTA: AN IMPORTANT BUT OFTEN NEGLECTED TOOL FOR NEONATOLOGISTS

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The placenta, a vital interface between mother and fetus, is a fundamental organ for the development of a physiological pregnancy and its functions should be preserved throughout the course of gestation. Alterations in the placentation process will have an impact on fetal well-being and will result in pregnancy complications. There are still important knowledge gaps in neonatal and perinatal medicine regarding the consequences that placental alterations might have upon newborns' health.

“Fetal programming of adult diseases” means that conditions that perturb the placental environment during pregnancy cause maladaptive changes in the fetus that might, in the end, predispose the newborn to develop diseases later in life (i.e., hypertension, metabolic syndrome). The analysis of placental histology may help in the identification of unfavorable conditions in intrauterine life and may contribute to an early stratification of a heterogeneous population of newborns with a better perception of the risk of diseases in postnatal life.

Recent evidence points to a connection between oxidative stress (OS) and fetal programming; it is well known that OS plays a role in the pathogenesis of pregnancy complications and it has been demonstrated that hypoxia and inflammation may regulate placental development and function through OS, with plausible effects on fetal programming.

Gaining insight into the cellular and molecular mediators (i.e., Reactive Oxygen Species) associated with complications of pregnancy will be essential for the proper understanding of the pathogenesis

of such complications and the development of successful intervention and prevention strategies. Given the link between OS and fetal programming, these strategies may, in the long run, help in the prevention of adult diseases. The development of a single or a panel of specific OS biomarkers in addition to histological analysis of the placenta may assist the clinicians in the management of newborns suffering from intrauterine insults.

Neonatologists should grow more aware of the importance of a physiologic intra-uterine environment and of the complexity and fascinating long-term impact that a transient organ such as the placenta might have on the future development of newborns.

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LECT 7

VITAMINS TODAY: FOCUS ON NEONATOLOGY

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INTRODUCTION

Vitamins are bioactive molecules that are essential to life in very low amount and as such, are classified as micronutrients. As humans have no or limited capacity for endogenous production, they need to acquire vitamins from diet regularly. Vitamins are involved in a multitude of biochemical reactions as well as in cellular and physiological regulatory processes. The functional spectrum of vitamins is broad and ranges from protection against oxidative damages to cellular division, energy, and one-carbon metabolism to mention a few. If consequences of vitamin deficiencies are well reported, there are knowledge gaps in what are the health consequences of suboptimal vitamin levels on human health at every life stage. Also, it is still unclear whether the available reference levels for vitamin biological status are appropriate to every age groups, ethnicity, and clinical conditions. There

is thus a need to invest research efforts to study the biology of vitamins and its related health effects in specific individual groups and particularly in newborns.

MATERIALS AND METHODS

A systematic review and meta-analysis of observational studies and randomized controlled trials on vitamins in neonatology field were conducted.

RESULTS

Most of the studies address single vitamin at once that is hampering the possibility to develop new knowledge on vitamins as a micronutrient system. This is in part because most of the vitamin status biomarkers are determined using blood-based assays and that availability of the required blood volume for such analyses is limited in newborns. There are also important knowledge gaps in understanding the molecular networks between vitamins, gut microbiota, and the host physiology.

CONCLUSIONS

Novel technological approaches to assess the vitamin status of the newborn are necessary to enable acquisition of information on vitamins as a micronutrient system as well as to investigate vitamin nutritional requirements under different clinical conditions. The gut microbiota-vitamin axis remains an important field to be explored to understand the molecular relationships between micronutrient intake, status, and the establishment of a healthy gut microorganism ecosystem.

LECT 8

PERSISTENT DUCTUS ARTERIOSUS: THE ITALIAN EXPERIENCE AND MORE

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INTRODUCTION

Patent ductus arteriosus (PDA) is a frequent complication in preterm infants with respiratory distress syndrome (RDS) and 60% to 70% of preterm infants of < 28 weeks' gestation receives medical and/or surgical treatment for PDA. However, infants born at 23-24 weeks' gestation have the highest risk of developing a hemodynamically significant patent ductus arteriosus (hsPDA), that is refractory to

pharmacological closure requiring surgical ligation. Thus, these patients might have the greatest benefits from hsPDA closure, although previous studies on PDA closure were not focused on this population.

MATERIAL AND METHODS

We carried out a retrospective multicenter study at 13 third level Italian Neonatal Intensive Care Units to compare the occurrence of hsPDA, the failure rate of the first course of ibuprofen in closing hsPDA, and need of surgical closure in infants born at 23⁺⁰-24⁺⁶ weeks' gestation to those in infants born at 25⁺⁰-28⁺⁶ weeks' gestation. All infants underwent echocardiographical assessment for hsPDA diagnosis and eventually pharmacological treatment, and surgical closure. Pharmacological treatment was performed with ibuprofen at a dose of 10 mg/kg followed, after 24 and 48 h, by 5 mg/kg i.v., or paracetamol at a dose 5 mg/kg/6h intravenously for three days i.v.

RESULTS

We studied a total of 842 infants, of which 562 (67%) developed a PDA. Among those with PDA, 511 (91%) received pharmacological treatment for a hsPDA. We found that a hsPDA occurred in 70% (106/151) of infants born at 23-24 weeks and in 59% (405/691) of infants born at 25-28 weeks of gestation ($p < 0.001$). Failure of closure with the first-treatment cycle (69 vs. 40%; $p < 0.001$) and need of surgical closure (19 vs. 10%) were more frequent ($p < 0.011$) in infants born at 23-24 than 25-28 gestational weeks. Paracetamol vs. ibuprofen treatment and gestational age of 23-24 versus 25-28 weeks increased closure failure, while less severe RDS and maternal clinical chorioamnionitis decreased it.

CONCLUSIONS

Among extremely preterm infants, infants born at 23-24 weeks of gestation have the highest risk of developing a hsPDA refractory to pharmacological treatment requiring surgical closure. Unexpectedly, about half of infants born at 23-24 weeks of gestational age and a quarter of infants born at 25-28 weeks of gestational age received paracetamol as the first-choice drug. This suggests that in our country many neonatologists prefer paracetamol due to similar effectiveness but less risk of adverse effects than ibuprofen. Our findings support the need for individualized more careful strategies for hsPDA management in this special population. Further studies might evaluate if a prophylactic approach with a safer drug, such as paracetamol, might be effective in limiting pharmacological unresponsiveness, preventing the need of surgical

closure, and, ultimately, improving the outcome of these special patients.

LECT 9

NATURE OR NURTURE? THE ANSWERS FROM THE INTERGROWTH-21ST PROJECT

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The INTERGROWTH-21st Project, funded by the Bill & Melinda Gates Foundation and led by the University of Oxford's Nuffield Department of Women's & Reproductive Health, had already shown that healthy, well-nourished women, free of disease, living in a clean environment and receiving good antenatal care have children with similar skeletal growth patterns inside the womb, at birth and up to the age of two. This research project produced a unique set of international standards for monitoring growth which perfectly match the existing WHO Child Growth Standards that are being used in virtually every country in the world [1, 2].

Recently, the international consortium of INTERGROWTH-21st researchers has found that attainment in early childhood of neurodevelopmental milestones (relating to cognition, language ability, and motor skills) is, like physical growth, very similar among children across diverse geographical and cultural settings, provided that their health and nutritional status are adequate [3]. The findings are unique because neurodevelopmental markers of early childhood have never been studied in this way before.

The researchers assessed 1,307 healthy 2-year-old children of urban, well-nourished, educated mothers enrolled in early pregnancy in Brazil, India, Italy, Kenya, and the UK, using a specially developed psychometric tool, standard visual tests and WHO motor milestones. In 14 of the 16 domains, the percentage of total variance that could be attributed to differences between populations ranged from 1.3% (cognitive score) to 9.2% (behavior score). This means that, across a comprehensive set of indicators of physical and early child neurodevelopment, less than 10% of the variability was based on the child's genes (nature) while the rest is environment (nurture).

Results of the Project have profound implications on international development policies since clearly show that environmental and social inequalities during pregnancy and early infancy have lifelong consequences on both individuals and countries.

In the multitude of diverse ethnic groups, nurture plays the most important role influencing not only health and growth but also neurodevelopment, thus providing an essential contribution to international planning of health and social issues.

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LECT 10

NEONATAL JAUNDICE: WHEN TO WORRY?

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Hyperbilirubinemia, presenting as jaundice, is a common and frequently benign condition in newborn babies. More than 85% of newborns develop some degree of jaundice during the first days of life. However, severe hyperbilirubinemia may cause brain damage when it is not recognized or is left untreated. The spectrum of neurologic sequelae is called "kernicterus spectrum disorder" (KDS), with acute bilirubin encephalopathy and its consequences at the end, and more subtle disorders at the other.

Worldwide, it is estimated that severe hyperbilirubinemia affects at least 481,000 late preterm and term newborn babies annually, resulting in 114,000 deaths and more than 63,000 survivors with moderate or severe long-term disability. In South Asia, severe hyperbilirubinemia is the seventh cause of neonatal mortality. Also, in high-income countries, an estimated 1 in 67,000 neonates develop classical kernicterus. Incidences of kernicterus spectrum disorder appear to have increased within the last decade. Early post-natal discharges, increased ratio of C/S deliveries, breastfeeding problems in the first days after delivery, a "gentler approach" to treatment and inadequate monitoring in the community could be contributing to severe hyperbilirubinemia.

Timely recognition of potentially severe jaundice, caused by hyperbilirubinemia is essential to prevent KDS. Transcutaneous bilirubin devices (TcB) have been developed as potential non-invasive alternatives to visual inspection. Studies have shown a good correlation between total serum bilirubin and TcB measurements. It is, however, important to note that selective screening based on visible jaundice still carries a risk of under-diagnosis and universal TcB screening may be a valuable approach to avoid this risk.

In the last decade, chronic bilirubin encephalopathy has been found to develop in preterm infants, because it can now be clinically diagnosed based on magnetic resonance imaging, abnormal auditory brainstem response, along with physical findings of kinetic disorders with athetosis. So, preterm hyperbilirubinemic babies, especially extremely preterm ones, should be evaluated and followed carefully for hyperbilirubinemia. Diagnosis and treatment criteria for hyperbilirubinemia should be revised in extremely preterm infants.

Although neonatal jaundice persisting beyond 14 days is a common clinical scenario usually with benign unconjugated hyperbilirubinemia, a group of neonates with conjugated hyperbilirubinemia and liver disease is included in this group. Early identification of liver disease improves the infant's outcome, especially for those with extrahepatic biliary atresia.

LECT 11

NEONATAL VENTILATION IN THE THIRD MILLENNIUM

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Although life-saving for the sickest infants, invasive mechanical ventilation (MV) has many undesirable side effects on the lung, brain, and cardiovascular system. The process of lung damage from MV is multifactorial and cannot be linked to any single variable. Volutrauma and atelectrauma have been identified as the most important and potentially preventable elements of lung injury. Volutrauma is injury caused by over-distention and excessive stretch of tissues, which leads to disruption of the alveolar epithelium, edema, proteinaceous exudate and release of proteases, cytokines and chemokines causing in turn biotrauma. Atelectrauma is lung injury due to tidal ventilation in the presence of atelectasis. Shear forces at the boundary between the aerated and atelectatic part of the lung cause tissue damage, while atelectatic areas determine an uneven distribution of ventilation. While using conventional MV, synchronization with infants' spontaneous breathing, volume-targeted ventilation, and the "open lung" concept (obtained by selecting proper PEEP levels) are the proven lung-protective ventilatory strategies. Comparing elective conventional MV and elective High-Frequency Oscillatory Ventilation (HFOV), a recent *Cochrane* review [1] showed that elective HFOV results in a small reduction in the risk of CLD, but the evidence is weakened by the inconsistency of this effect across trials. Moreover, the benefit could be counteracted by an increased risk of acute air leak using HFOV. About long-term outcomes, most trials have not identified any difference between these two invasive modes. For the reasons mentioned above, avoidance of MV in favor of non-invasive modes of ventilation remains the most important step in preventing neonatal morbidity. Nasal continuous positive airway pressure (nCPAP), heated humidified high flow nasal cannula (HHHFNC), bilevel nCPAP (BIPAP) and nasal intermittent positive airway pressure (NIPPV) are the most common and currently available non-invasive modes. In recent years, also nasal HFOV has been introduced in Neonatology. All these modes, however, offer infants a different degree of respiratory assistance. Non-invasive modes that apply to the airways a constant pressure, like nCPAP and HHHFNC, help infants to obtain and maintain an adequate

Functional Residual Capacity (FRC), thus reducing their work of breathing (WOB) through the improvement of the working condition of the respiratory system. These modes offer non-invasive respiratory support. Contrariwise, a variable pressure mode like NIPPV may actively influence the infant's ventilatory pattern by supporting spontaneous efforts with superimposed positive pressure breaths. This mode reduces infants' WOB and provides energy for ventilation, being a non-invasive ventilation mode. BIPAP uses small pressure differences between inspiratory and expiratory phases, but no evidence confers any advantage over CPAP, and any clinical difference may only reflect a higher mean airway pressure applied to the respiratory system. Nasal interfaces have also been used with HFOV, but results are still uncertain [2]. Performance and effects of NIPPV can be optimized by synchronizing mechanical breaths to spontaneous ones; different methods of triggering have been developed: the Graseby capsule, the neurally adjusted ventilatory assist (NAVA), and the flow-sensor [3]. Non-invasive techniques are being increasingly used in preterm infants with respiratory failure, and several trials seem to demonstrate that NIPPV and SNIPPV are more effective than NCPAP in reducing extubation failure, as the primary mode of ventilation and to treat apnoea of prematurity.

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LECT 12

METABOLOMICS AND MICROBIOMICS IN INFECTIONS

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INTRODUCTION

Although early diagnosis helps in the prompt and correct management of neonatal sepsis, improving survival and outcome, well-defined biomarkers are still lacking in clinical practice. Metabolomics is a promising all-in-one tool that helps to monitor modifications induced by sepsis, such as hypoxia, oxidative stress, and increased energy requests (modulating glucose and oxidative metabolism of fatty acids). In the literature, there are few available metabolomics data regarding metabolomics studies on neonates to detect the occurrence of sepsis precociously.

SEPSIS

Urinary metabolomics between septic neonates and healthy controls has been for the first time compared by our research group, demonstrating (through ¹H-NMR [nuclear magnetic resonance] and GC-MS) statistically significant differences. In particular, urinary metabolomic in infected neonates with Early Onset Sepsis and Late-Onset Sepsis showed increased levels of acetone, ketone bodies, including hydroxybutyrate and acetoacetate, glucose, maltose, lactate, and acetate, and lower levels of the TCA cycle, such as citrate, ribitol, ribonic acid, pseudouridine and 2-ketogluconic acid, 3,4-dihydroxybutanoic acid, and 3,4,5-trihydroxypentanoic acid. Therefore, it seems that sepsis modifies the metabolism of glucose and acetone ketone bodies, in addition to modifying oxidative stress pathways.

Serafidis et al. evaluated through ¹H-NMR and LC-MS/MS urine samples from neonates with LOS. The most involved metabolites were valine, phenylalanine, taurine, fumaric acid, pyruvic and lactic acid, glucose, and riboflavin, related to energy production and anti-inflammatory actions. Inosine and hypoxanthine also showed a small increase in septic neonates, probably due to sepsis-related cellular destruction and degradation.

The urinary metabolome has also been evaluated in n = 1 preterm neonate with invasive fungal infection using GC-MS; biomarkers as N-glycine, D-serine, L-threonine, D-glucose, and maltose increased in septic urine.

The main factors influencing the microbiome and metabolome resulted in nearly uniform antibiotic administration in the Neonatal Intensive Care Unit (NICU).

Moreover, in the study of Mickiewicz, serum metabolome from n = 60 septic pediatric patients (including seven newborns) was characterized by increased levels of lactate, glucose, creati-

nine, 2-oxoisocaproate, 2-hydroxysovalerate, and 2-hydroxybutyrate and lower levels of threonine, acetate, 2-aminobutyrate, and adipate if compared with n = 40 healthy pediatric controls (¹H-NMR), demonstrating that metabolomics could be useful in the diagnosis and prognosis of sepsis in the Pediatric Intensive Care Unit (PICU).

NECROTIZING ENTEROCOLITIS

It seems that there is an essential role of gluconic acid. When an external administration of Ca gluconate (i.v., os) is excluded, gluconic acid is related to increase production by the organism due to spontaneous oxidation of glucose by the microbiota: *S. fecalis*, *Pseudomonas spp.*, *E. coli* (Entner-Doudoroff pathway not used by healthy flora). The species producing and using gluconic acid have the stronger proliferative ability, stronger virulence, and strong drug-resistance. In preterm neonates exposed to histological chorioamnionitis, we performed a pilot study suggesting a strong impact of gluconic acid, which is the only elevated metabolite among the first 30 essential metabolites.

CONCLUSIONS

A strong association exists between metabolomics and microbiomics in several perinatal pathologies. Metabolomics is considered the Rosetta Stone of microbiomics. Significant results are available in Perinatal Medicine. Further studies are needed to understand the secret languages between bacteria and the organism. Metabolomics is highly promising in the perspective of an early diagnosis without any false-positive or false-negative results, tailored management, and even for monitoring disease progression and antibiotic toxicity. Metabolomics could rapidly become the “new clinical chemistry”, presenting not only a power of discrimination but also a power of prediction. We are preparing atlases of pathologies in Neonatology, from metabolites to diseases.

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LECT 13

HUMAN BREAST MILK METABOLOMICS

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Human breast milk (HBM) is the natural and ideal food for infants. In addition to the classical nutrients, such as proteins, carbohydrates, lipids, vitamins, and minerals, milk contains several bioactive components. Among them, there are growth factors, anti-microbial components, and stem cells, which can integrate *in vivo* in the tissues of the neonate and differentiate in mature cells. HBM has the characteristic of significantly varying from one woman to another, and it changes continuously during lactation to adapt to the growing energy needs of the developing infant. Different maternal, environmental, and genetic factors influence the biology beyond these modifications, but their roles are still unclear and under investigation.

The application of metabolomics to HBM is an exciting and emerging field, offering an approach to investigate the complex relationships between nutrition and infant's health. Although still in the early stage of development, these investigations evidenced the potential of metabolomics as a key technology to improve understanding of the biochemical heterogeneity of breast milk.

Here, the main results from metabolomics investigation of HBM metabolome are discussed with specific emphasis on oligosaccharides, the third most abundant constituent of maternal milk that provides multiple benefits to infants, including prebiotic effects, gut maturation, antimicrobial activities, and immune modulation.

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LECT 14

HUMAN MILK MICROBIOME

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A large number of biologically active components have been found in human milk (HM); among them, microbiological agents seem to have a pivotal role. Both in human and animal models, studies have provided strong evidence that HM composition can be modified by maternal exposures during pregnancy, subsequently influencing health outcomes for the breastfed child. Evidence varies from the research studies on whether breastfeeding protects the offspring from non-communicable diseases, including those associated with immunological dysfunction such as autoimmune, asthma, eczema, coeliac diseases. It has been hypothesized that the conflicting evidence results from HM composition variations, which contain many immune active molecules, oligosaccharides, lactoferrin, and lysozyme in differing concentrations, along with a diverse microbiome. We have demonstrated that microbiome is different among populations being probably influenced not only by the environment but also by diet, social habits, drug consumption. Another major variable influencing the microbiome, characterizing the HM, is the mode of delivery: this can determine the intestinal microbiome of the offsprings but also the HM microbiome, giving from the early period of life different stimuli to the newborn's immune system. Further work is necessary to understand the factors influencing the composition of HM microbiome and to elaborate a strategy (diet, supplementation...) to drive the correct microbiome.

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LECT 15

GROWTH FACTORS IN MATERNAL MILK

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Human milk (HM) is a unique complex biological product, the ideal source of nutrition for infant feeding, playing a vital role for optimal neonatal growth and development. It contains a wide range of nutrients and biologically active factors and protects against infections, allergies, and later development of metabolic disorders. The role of bioactive components in HM is an emerging topic in nutritional research.

Among bioactive components in HM, growth factors are of utmost importance due to their implication in growth, maturation, and integrity of several organs (particularly of the neonatal gastrointestinal tract), gut immunity and anti-inflammation. The highest concentrations of growth factors are found in colostrum.

Growth factors in HM comprise:

1. Hepatocyte Growth Factor (HGF), released into HM by multipotent mesenchymal stem cells. Through paracrine and endocrine signaling, it promotes organogenesis and preserves proliferation, angiogenesis, and intestinal tissue development.
2. Epidermal Growth Factor (EGF), contributing to normal intestinal cell development. Heparin-binding growth factor (HB-EGF), member of the EGF family, protects from intestinal ischemia-reperfusion injury, hemorrhagic shock, and NEC. EGF concentrations, being higher in preterm HM, decrease with prolongation of lactation.
3. Neuronal Growth Factors: brain-derived neurotrophic factor (BDNF), S100B protein, and glial cell line-derived neurotrophic factor (GDNF) significantly contribute to neuronal survival and proliferation of the nervous system. Increased concentrations of HM S100B protein and GDNF are documented within the lactation period.
4. Insulin-Like Growth Factor (IGF) Superfamily (IGF-I and IGF-II). IGF-I concentrations in HM are higher in colostrum and lower in mature HM.
5. Vascular Endothelial Growth Factor (VEGF), also controlled by IGF-I, mediates vascularization and its concentrations are higher at the beginning of the lactation period.
6. CD14 Protein is considered to protect against allergic manifestations and eczema development.

Some adipocytokines, like leptin, adiponectin, and ghrelin in HM, may contribute to infant growth.

LECT 16

MOTHERS' QUESTIONS ON MATERNAL MILK

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Before starting to describe all the hypothetic doubts concerning breastfeeding that a new mother and a new father can have in the first months of life of their newborns, one fundamental concept must be premised: there is no rule for everybody, there is no unique protocol to use for every neonate.

Since each infant is different, each mother is different and each family is different. On the other hand, it is true that there is some general information that can help the parents to know their children and manage some apparently difficult situations, that are part of the child's growth. It is essential to be able to use this information and apply the most suitable suggestions to their child. Nobody can know newborns better than their parents: maternal and paternal instincts do not almost ever make a mistake. They only need to be informed and begin on the base of knowledge that can accompany and make more serene the wonderful path of the first period of life and growth of a newborn. Maternal milk is a complex fluid that evolutionary adapted to satisfy the nutritional needs of the neonate. In addition to the classical nutrients such as proteins, carbohydrates, lipids, vitamins, and minerals, milk contains several bioactive components. Among them, there are growth factors, anti-microbial components, and stem cells, which can integrate *in vivo* in the tissues of the neonate and differentiate in mature cells.

Breast milk has the characteristic to vary from one woman to another significantly, and it changes continuously during lactation to adapt to the growing energy needs of the developing infant. The variable components of milk include oligosaccharides that represent the third most abundant constituent. They exert several essential functions, such as the modulation of the composition of the gut microbiota that influences a wide range of physiological processes in the neonate.

The application of metabolomics in Neonatology offers an approach to investigate the complex relationship between nutrition and infant's health. The characterization of the metabolome (the whole set of metabolites) of the breast milk compared to formula milk allows understanding how each nutrient affects the neonate's metabolism and offers the chance to intervene on the composition of the diet according to the nutritional request of the neonate. Human milk has a metabolic function, the glycobiome of some *Lactobacilli* and *Bifidobacteria*, including some species isolated from the milk, can help to create

a specific microbiota in the neonate. Moreover, maternal milk has a buffering capacity, that allows acidifying the intestinal content in order to make it more fermentable by the bacteria of the proximal colon, and it has an inhibitory effect on the growth of *Clostridium spp.*, *Bacteroides*, and other anaerobic bacteria. The type of nourishment in the first months of life seems to be the most important determinant of the individual's health, and its protective action occurs with the modulation of the intestinal microbiome. Thus, the composition of the microbiota in human milk has significant consequences on the colonization of the intestine both in the short and long-term for the health of the neonate. The future of research can be related to metabolomics, milk microbiota, and stem cells. Probably from the integration of these three fields, it will be able to take significant steps forward in understanding the composition and functions of breast milk.

Nevertheless, new mothers and new fathers have several questions concerning breastfeed, which do not include only the composition of breast milk.

According to our experience in the SOS MAMI ambulatory at the Policlinico of Monserrato, here are the most common: “Is it important to breastfeed?”, “Should I test my milk in order to check if it is nourishing enough?”, “Should he/she latch on the breast immediately?”, “I had a cesarean section, so probably the rise of the milk would not happen?”, “The baby cries when I offer him/her my breast: is it possible that he/she does not like my milk?”, “How can I latch him/her on the breast and avoid his/her inconsolable cry?” These questions are the demonstration of how delicate is this moment for all families, and the professionals must be well aware of all the difficulties and doubts that new parents can experience and be ready to take care of them in the best possible way.

LECT 17

THE ROLE OF THE MIDWIFE

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The figure of the midwife is not completely determined because only recently it was realized that midwife role is not generally confined to the delivering babies moment or associated with women gynecological problems. A midwife is usually the first and main contact for the woman during her

pregnancy, throughout labor and the early postnatal period. Midwives now should carry out clinical examinations, provide health and parent education, and support women and their families throughout the childbearing process to help them adjust to their parental role. The midwife should work in partnership with other health and social care services to meet individual women's needs, offering news hospitals obstetric services, for example, promoting and supporting breastfeeding is an integral part of the role of the midwife. She is responsible for providing care and supporting women to make informed choices about breastfeeding program.

In particular midwives should be able to: (1) describe the physical and emotional health benefits of breastfeeding for children and their mothers and how breast milk optimizes brain development and promotes secure primary attachment; (2) increase the understanding of how babies can find the breast, why good attachment and positioning enable effective milk transfer, and how demand feeding helps babies regulate their own milk supply and learn appetite control; (3) describe breastfeeding challenges, their treatment, and prevention; (4) interpret changes in growth velocity and slow or rapid weight gain in breastfed babies and the importance of exclusive breastfeeding; (5) appreciate the importance of psychological support, and the role of breastfeeding peer supporters.

Breastfeeding self-care programs to increase breastfeeding self-efficacy after childbirth, and to facilitate the continuation of breastfeeding should be encouraged.

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LECT 18

LONG-TERM BENEFICIAL EFFECTS ON MOTHERS OF BREASTFEEDING

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Breastfeeding (BF) is associated with good physical and emotional health for the mother during the puerperium and the lactation periods. There are also long-term benefits induced by BF for mother health. As for oncological diseases, many pieces of evidence demonstrate that BF reduces the risk of breast, ovarian, and endometrium cancers. The risk of breast cancer can be reduced by more than 4% for each year of BF. The relative risk of developing ovarian cancer is estimated to be reduced by 2% for each month of BF. An extended period of BF is associated with a reduced risk of endometrial cancer. Another gynecological disease negatively influenced by BF is the endometriosis.

Similarly to the above oncological diseases, endometriosis depends on the cyclical ovarian hormones, and it is known that BF abolishes the cyclical ovarian function through interferences on hypothalamic factors regulating the secretion of gonadotropins, the directors of ovarian function. It is also known that BF for prolonged periods reduces the risk of metabolic syndrome. In particular, one of the most important mechanisms involved in this occurrence is the reduced insulin resistance (IR). The mechanism through which BF reduces the risk of IR and type 2 diabetes is related to the increase of oxytocin during the BF. In fact, it has been demonstrated that oxytocin reduces IR. There is an inverse and dose-dependent association between BF and type 2 diabetes. The oxytocin could play an important role in the reduced risk of BF on some inflammatory diseases, such as rheumatoid arthritis, Alzheimer disease, and multiple sclerosis. Similar to the hypothalamic-pituitary-adrenal axis, the oxytocin-secreting system closely interacts with the immune system, integrating both neurochemical and immunologic signals in the central nervous system and in turn, affects immunologic defense, homeostasis, and surveillance. In this manner, the oxytocin system counteracts with the action of prolactin, of which the immunostimulatory effect is so well known that BF can be contraindicated in subjects with autoimmune disease although the oxytocin anti-inflammatory role. Further studies will clarify whether in addition to oxytocin, during BF, there are other factors involved in the regulation of the immune system.

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LECT 19

OBSTETRICAL MONITORING TO PREVENT PERINATAL ASPHYXIA

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Perinatal asphyxia (PA) is defined as an oxygen deprivation that occurs around the time of birth. Perinatal events such as maternal or fetal hemorrhage, intermittent or acute umbilical cord compression, uterine rupture or shoulder dystocia could reduce the supply of oxygenated blood to the fetus. PA is a general term referring to neonatal encephalopathy related to events during birth leading to neurological conditions or impairment of different organs and systems. It is often interchangeably used with terms describing the neonatal sequelae such as hypoxic-ischemic encephalopathy and cerebral palsy (CP). Therefore, the pathological mechanism is still not precise and a standard golden treatment has not still be defined. The majority of cases of PA occur intrapartum, although 20% occur antepartum and other cases occur in the early post-natal period.

In this review of the literature, we have collected most ways of intrapartum, antepartum, and postpartum screening and diagnosis of PA. The literature revealed that neonatal and intrapartum related factors like breech presentation, mode of delivery, meconium-stained amniotic fluid, prolonged rupture of membrane, prolonged labor, birth weight, and prematurity of the newborn were found to be significant factors for birth asphyxia.

For the intrapartum diagnosis and screening, the electronic fetal heart monitoring (EFM) during labor has been designed to prevent PA although it has a very low positive predictive value and for this reason, it should be accompanied by fetal scalp stimulation and fetal electrocardiogram analysis.

For the antepartum diagnosis and screening, antenatal fetal testing like contraction stress test

(CST), no stress test (NST) and biophysical profile BPP has been developed to prevent the risk of intrauterine injury or death in pregnancy at high risk.

After delivery, the diagnosis and screening of PA include the placental histologic examination and umbilical cord gas analysis with lactate.

Nevertheless, most PA cases are caused by conditions unrelated to labor. When asphyxia occurs in an intrapartum event, it is usually due to an obstetric emergency. For these emergencies, prompt intervention and delivery are imperative. Our ability to predict intrapartum asphyxia remains poor. Strategies such as high-risk screening pregnancies, scalp stimulation for indeterminate fetal heart tracings, intrauterine resuscitation, and expeditious delivery may aid in the diagnosis and prevention of PA. Future research should focus on diagnostic methods for predicting metabolic acidosis before it occurs, and appropriate interventions for its management.

LECT 20

PERINATAL ASPHYXIA IN TERM NEWBORNS

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Despite considerable progress in perinatal care in the past decades, perinatal asphyxia (PA) still leads to significant mortality and morbidity. PA is an impairment of placental (prenatal) or pulmonary (immediate post-natal) gas exchange resulting in progressive hypoxemia and hypercapnia. Accordingly, the tissues and vital organs will develop an oxygen debt, with subsequent lactic acidosis. PA may result in systemic effects, including respiratory distress, pulmonary hypertension, and myocardial, renal and liver dysfunction, although hypoxic-ischemic encephalopathy (HIE) is the clinical condition exhibiting the most severe sequelae. The incidence of PA is about 1-6/1,000 live term newborns, and it still represents the third cause of neonatal death, after preterm birth and infections. Among affected infants, 15-20% die in the first month of life, and about 25% develop permanent neurological deficits.

There are many risk factors for PA, and it may occur antepartum, intrapartum, or in the early postnatal period. Clinical and laboratory criteria for the diagnosis of intrapartum asphyxia are still debated. A statement of the American College of Obstetrics and Gynecology included 4 essential criteria and 5 additional criteria. However, the cornerstone of this statement and others is the presence of severe metabolic acidosis (pH < 7.0 and base deficit ≥ 12 mmol/L) at birth in combination with early signs of moderate or severe encephalopathy.

In the pathophysiology of HIE, there are 3 stages of brain injury: (1) immediate primary neuronal injury: the interruption of oxygen and glucose to the brain leads to intracellular acidosis, ATP decrease, failure of the ATP-dependent NaK pump and subsequent cell death; (2) reperfusion: during this latent period of about 6 hours, reperfusion occurs, and some cells recover; (3) late secondary neuronal injury: it occurs over the next 24-48 hours, when the injured regions are reperfused and damaged cells lyse, thus spreading toxic neurotransmitters and widening the brain areas affected. Clinically, the severity of HIE may be determined using the Sarnat staging, which ranges from Stage I (mild) to Stage III (severe).

Therapeutic hypothermia (TH) is the most effective treatment for HIE. Its goal is to intervene during the latent period to minimize damage from the secondary neuronal injury. TH has multiple neuroprotective effects and is applied in selected newborns meeting specific inclusion criteria. When started within 6 hours of injury, TH reduces mortality and severe disability from 62% to 48% and increases survival with the normal outcome from 24% to 40%. Infants with moderate HIE (Sarnat Stage II) benefit most from TH. The treatment of pulmonary hypertension, respiratory distress, myocardial dysfunction, and coagulopathy is supportive. The prognosis depends on the severity of PA: only a minority of newborns with severe HIE survive without handicap.

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LECT 21**MITOCHONDRIA ASPHYXIA: THE ATP SYNTHASE AS A TARGET FOR ISCHEMIA AND REPERFUSION INJURIES**

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The detrimental consequences of perinatal asphyxia are primarily dependent on the most oxygen demanding intracellular compartment: mitochondria. These organelles, which coordinates energy balance with cell death regulation, deeply influence cell survival in both hypoxic phase as well as in the reperfusion phase. During hypoxia, mitochondria cannot supply neural ATP demand and undergo remodeling which favors a switch to anaerobic respiration. Nonetheless, greatest cellular damage occurs at the time of reperfusion. The rapid elevation of oxygen does not allow mitochondria to further adapt and predispose for the induction of mitochondrial permeability transition (MPT). This refers to an abrupt increase in the permeability of the inner mitochondrial membrane to low molecular weight solutes. Widespread MPT has catastrophic consequences for the cell, de facto marking the boundary between cellular life and death. MPT results indeed in the structural and functional collapse of mitochondria, an event that commits cells to suicide via regulated necrosis or apoptosis. Though its relevance to pathological conditions is well established, the composition and mode of action of the supramolecular entity that initiates MPT (the permeability transition pore complex [PTPC]), remain to be elucidated. We already demonstrated that PTPC involves the conformational rearrangements of the F1FO ATP synthase and especially of its C ring. Indeed, genetic manipulation of the C subunit (the subunit composing the rotor of the complex) can dramatically impair or potentiate MPT induction.

Based on the evidence, we generated a novel class of compounds that targets the c subunit of the F1/FO-

ATP synthase complex with good PTPC inhibitory and preserved the mitochondrial ATP content despite interacting with the ATP synthase complex. In a model of myocardial ischemia/reperfusion injury, the compounds resulted beneficial, including a decreased apoptotic rate in the whole heart and overall improvement of cardiac function upon administration during reperfusion.

Ultimately, preliminary data suggest the involvement of the ATP synthase/PTPC axis in neonatal asphyxia, which may provide a significant target for the treatment of this condition.

LECT 22**PERINATAL ASPHYXIA: MEDICAL-LEGAL ASPECTS**

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The incidence of neonatal encephalopathy is still elevated in all the international context, reaching its incidence of roughly 3 per 1,000 live births. Although an in-depth debate about the true meaning of such a definition is still on-going, the aforementioned definition, only for the aim of this paper, will encompass both neonatal encephalopathy and hypoxic-ischemic encephalopathy. To better say, the comprehensive use of HIE label may be responsible, in the malpractice scenario, to a fallacious judicial misunderstanding of the underlying cause. Lay people may understand that a hypoxic event surely occurred during the perinatal period (labor and the first 6 gold hours after the delivery) and, if so, midwives and physicians may be considered responsible of the relevant neurological damage suffered by the newborn. The identification of the true biological cause of perinatal asphyxia is instead a conundrum, not fully understood yet. Without a scientifically sound demonstration of the true biological cause of the encephalopathy, it may become hard to imagine the dutiful clinical behavior required to the health professionals. In this medical and legal context, huge efforts have been in the last years devoted to the biological comprehension of the several causes of perinatal asphyxia and the identification of one or more biomarkers related both to the cause of the neurological damage and to the clinical outcome of the newborn. This issue

has been investigated using all the “omics” sciences, seeming transcriptomics and metabolomics the more promising, being a priori able to intercept the whole biological response of the body – and mainly of the brain – to a hypoxic damage (in blood for both the approach and also in urine and in cerebrospinal fluid when a metabolomics approach is employed) and even to describe the biological trajectory that each individual follows from the first moment after the birth up to the first 72 hours after the therapeutic hypothermia treatment. All the experimental results – eventually obtained by animal models and validated in wider and wider cohorts of newborns – may be in a next future implemented in the legal scenario in order to deny – at least – or affirm – at best – the causal relationship between personal damage suffered by the newborn and professional (mis)conduct. A robust negative predictive value of the analysis would help in the Court to avoid wrongful conviction of a health professional, while a positive predictive value – whenever achievable by the ‘omics’ approaches under investigations – will be considered one (good) piece of evidence to be evaluated by the medico-legal expert, by the lawyers, and by the judge, in the light of all the others evidence collected during the lawsuit. It has to be considered that in several juridical contexts – and the Italian one among the others - in a civil lawsuit the evidentiary standard requested in cases where the biological cause of damage is not certain is the preponderance of the evidence. To decide in favor of the claimant, the judge has to decide that the burden of proof has been met whenever the party with the burden convinces the fact finder that there is a greater than 50% chance that the claim is true. To reach such a chance – or to deny the relationship between the damage and the professional behavior – all the evidence play an essential role, but the ‘biological’ ones may turn out to be sounder when compared with testimonials. In this perspective the recent metabolomics results obtained by several research groups looking for single biomarkers (eg lactate), or metabolite index/score (eg ratio among succinate, glycerol, 3-hydroxybutyrate and O-phosphocholine – or choline, 6,8-dihydroxypurine, and hypoxanthine) or a metabolomics profile seem to pave the way for the implementation of helpful biological tools to unravel this complex medico-legal issue.

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LECT 23

PERINATAL ASPHYXIA: PATHOLOGICAL ASPECTS

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Despite major improvements in perinatal care, perinatal asphyxia remains one of the 3 major causes of neonatal death. As a consequence, asphyxia and its consequences are the main targets of perinatal pathologists involved in the study of the cause of death of newborns. Oxygen deprivation and lack of perfusion due to asphyxia lead to several pathological changes in multiple organs. Among these, a major role is played by hypoxic-ischemic encephalopathy and sequelae, occasionally leading to the insurgence of the multi-organ dysfunction syndrome. The most important pathological markers of asphyxia in the perinatal setting are represented by the endothelial lesions, including endothelial swelling, apoptosis, detachment, and eventually loss of the endothelial barrier. These asphyxia-related endothelial changes may occur in all the organs. The loss of the endothelial barrier is often followed by platelet aggregation and thrombosis, ending with major tissue hypoxia and tissue damage. At the ultrastructural level, perinatal asphyxia is associated with a decrease in glucose and oxygen, followed by mitochondrial loss of function and ATP depletion. Pathological changes in the newborn affected by asphyxia are not restricted to oxygen deprivation. Reoxygenation and reperfusion may be followed not only by the restoration of oxygen supply but also by the activation of detrimental biochemical pathways, leading to endothelial and neuronal cell death. In particular, the formation of reactive oxygen species following reoxygenation may be detrimental for neurons and glial cells, leading to apoptotic cell death and the subsequent neurological

damage, the most important consequence of perinatal asphyxia. The finding of increased hepatic hemopoiesis, due to the increased levels of hypoxia-inducible factor following asphyxia, represents, for the prenatal pathologist, a marker of systemic tissue hypoxia. In conclusion, the accurate histological analysis of all the organs, in expert hands, may give to neonatologists relevant data for reaching an accurate clinical-pathological diagnosis in all asphyxiated newborns. In our experience, the accurate study of endothelial changes in all organs is the most important tool for the definition of the entity and diffusion of asphyxia-induced damage in the newborn.

LECT 24

IMPACT OF THE ECONOMIC CRISIS ON PERINATAL PARAMETERS AND LONG-TERM EFFECTS

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It is well known that economic crises have an impact on psychological and behavioral morbidity. Job losses, which predominately happen during an economic crisis, and poor socioeconomic circumstances in the families, increase the risk or severity of depression, anxiety, alcohol consumption, violence, and self-destructive behavior.

Children are a vulnerable population group, and there is a strong link between socio-economic living conditions and child health. Exposure to poverty in early life/during childhood for prolonged periods has a strong and irreversible impact on the physical, cognitive, and social health of children.

Several countries mainly of the European South, as Portugal, Spain, Greece, that suffered severe economic crises and implemented high levels of austerity, experienced adverse perinatal outcomes, particularly, increase in low birth weight and premature infants, advanced mean maternal age at delivery (over 35 years old) and increased percentages of cesarean sections.

According to the Developmental Origins of Health and Disease (DOHaD) concept, non-communicable diseases (NCDs), like obesity, type 2 diabetes mellitus, cardiovascular disease, endocrine cancers, osteoporosis, mental health and cognitive function disorders, respiratory disease, immune function and allergy, may have their origins in pre-conceptional,

prenatal, and/or early postnatal periods. Economic status influences environmental conditions *in utero* and in early childhood, which contribute to increased risk for subsequent early and later onset NCDs. Environmental insults during pregnancy to a mother (F0 generation) might affect not only the developing fetus (F1 generation) but also the germ cells which will go on to form the F2 generation. Although transmission of effects goes mainly through the maternal line, some effects take place through the exposure of the father to a stressor.

An adverse intrauterine environment leads to “early programming” with later DOHaD effects. Suboptimal nutrient supply and maternal undernutrition, consequent to an economic crisis, may lead to low birth weight infants, either preterm or intrauterine growth restricted (IUGR), who are at risk for cardiovascular and renal disease, central adiposity and insulin resistance, asthma and obstructive airway disease, mental and cognitive problems, as decreased intelligence quotient, attention deficit hyperactivity disorder, mood, anxiety, psychotic, and personality disorders later in life.

LECT 25

UNRAVELED MYSTERIES OF THE NEONATAL KIDNEY

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THE NUMBER OF NEPHRONS

In the kidney, the nephrons are the functional unit formed by the glomerule (the “prima ballerina” of the kidney), the tubule (composed of the most highly specialized cells of the organism after the cerebral neurons), blood vessels, and finally the interstice in the middle. The nephrons are hard workers who toil in silence 24 h a day and are extremely important for the entire organism since they remove a part of the body's wastes.

The number of nephrons varies from 200,000 to 2.5 million and this is considered normal for a person. Let us consider three term newborns (but we could also say three children or adults general), the first with 200,000 nephrons, the second with a million, and the third with 2.5 million. If we perform the creatininemia is normal: thus, the kidney function is considered regular. If there has been acute kidney

injury that “kills” 100,000 nephrons as the result of hyponutrition, hypo-oxygenation, or a drug that is harmful to the kidney. In the first neonate, this corresponds to the loss of half its nephrons. This means that in the pediatric age, he will have chronic renal insufficiency. In the second neonate, the damage corresponds to one-tenth of its nephrons (long-term kidney damage in adulthood or old age). For the third neonate, this loss is insignificant in the short and long term. We have to take into account something often underestimated: that of the basal variability between one patient and another and their variability after eventual treatment.

THE INTERRUPTION OF NEPHROGENESIS AND THE NUMBER OF PODOCYTES

Many factors can influence the interruption of nephrogenesis processes: chorioamnionitis, steroids, maternal diabetes, preeclampsia, IUGR. These events can result in preterm birth with blockage of nephrogenesis. The histological study of the kidneys in preterm newborns at different gestational age, allows us to calculate the radial glomerular count by counting the layers of glomeruli along a straight line extending from the renal capsule to the deepest area of the cortex; this study demonstrates marked interindividual variability related to different etiological agents (drugs or other stressors). The number of podocytes decreases when related to factors such as drug use or maternal diet. A low number of podocytes may represent a predisposing factor for the development of podocytopathies in adult life.

KIDNEY PROGRAMMING

Can glomerulogenesis, which generally comes to an end at 35 or 36 weeks of gestation, continue postnatally in a VLBW or ELBW newborn? Can the unnatural environment in which a baby with these characteristics finds itself alter glomerulogenesis and cause a reduced final number of nephrons? How is the kidney function of these babies a long time after birth? Preterm birth negatively influences nephrogenesis and glomerulogenesis: nephrogenesis is possible postnatally only for a maximum of 6 weeks after preterm birth. So, for example, if a baby is delivered prematurely at 24 weeks of gestational age, its kidney may have an increase in the number of glomeruli for 6 weeks only: at 30 weeks of postconceptional age (24 plus six after birth), glomerulogenesis for that neonate stops and cannot continue to the 35th or 36th week, the natural term for kidney development in a healthy pregnancy. If the neonate has suffered an acute kidney injury (for example due to asphyxia)

this period of kidney maturation is shortened. In the neonatal period, no problem may come to the fore, but when the child grows, a chronic kidney insufficiency could arise.

KIDNEY REGENERATIVE MEDICINE

Up to now, all researchers have focused on what inhibits nephrogenesis. Why not instead concentrate our attention on what favors nephrogenesis in the preterm neonate? The kidney maintains a delicate balance between protective and aggressive mediators. We can imagine that we can influence nephrogenesis (prolonging the period of nephrogenesis and increasing the production of nephrons at the right time, or possibly both options) by releasing the brake to reduce or inhibit programmed cell death (apoptosis), and by acting on the accelerator to favor the processes of cell replication (mitosis). Moreover, the kidney also contains stem cells, and we can imagine to use them to improve the prognosis of patients affected by kidney insufficiency. The kidney is abundant in stem cells and not only during the active phases of nephrogenesis, where we find many stem cells in the blue stria and the mesenchymal cap but also in the kidney of 38-41 week of gestation and kidney of adult life. In the mature kidney, the stem cells are found in the renal capsule, in the Bowman capsule, in the cortical interstitium, in the renal papilla and the hilum.

KIDNEY, METABOLOMICS AND MICROBIOMICS

Kidney disease can upset the delicate equilibrium between symbiont (“good”) bacteria and pathobiont (potentially “evil”) bacteria within the intestinal lumen. We know that bacterial metabolites, such as phenols, indoles, and amines, can contribute to the progression of an advanced chronic kidney disease and induce kidney injury, and that some of these metabolites, such as p-cresol and indoxyl sulfate, are associated with the diet-microbiota interaction.

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LECT 26

MANDATORY VACCINATIONS IN EUROPEAN COUNTRIES, UNDOCUMENTED INFORMATION, FALSE NEWS, AND THE IMPACT ON VACCINATION UPTAKE

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High rates of vaccination coverage are essential in preventing infectious diseases. Enforcing mandatory vaccinations is one of the strategies that some countries adopted to protect the community when vaccination coverage is not satisfactory.

In Italy, in 2017, vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliovirus, Haemophilus influenzae type b, measles, mumps, rubella, and varicella became compulsory in childhood. In order to contrast vaccination policies, anti-vaccination campaigns contribute to the spread of fake news. Among them, there is false information that Italy is the only country with a mandatory vaccination policy.

Not only in Italy, but vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliovirus, Haemophilus influenzae type b, measles, mumps, rubella, and varicella is also mandatory in children under 18 months. Other European countries adopted compulsory policies in order to prevent the spread of infectious diseases and to protect the community. Particularly in France, in 2018, 11 vaccinations became compulsory. During 2019, also other Countries in Europe are adopting mandatory vaccination policy.

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LECT 27

CHRONIC COUGH IN CHILDREN: DIAGNOSTIC AND MANAGEMENT APPROACH

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Cough during childhood is very common and is one of the most frequent reasons for consultation in daily pediatric practice. Cough is the way we defend ourselves from secretions, inhalation, or aspiration of some substances. It is a nonspecific symptom that occurs in varying situations, different from adult to child. Cough is often an unpleasant manifestation of benign affections. There are situations when it can be the only and/or first manifestation of a respiratory disease with important consequences in terms of morbidity and mortality when ignored.

Most of the time, the cough that occurs in childhood can be caused by infections that interest the upper and/or lower respiratory tract (bronchiolitis, pneumonia, convulsive cough). Sometimes it is caused by allergies, foreign body aspiration, or some chronic conditions at the onset. The child's cough differs from that of the adult through: duration (acute, subacute, chronic), a type of inflammation (neutrophilic, eosinophilic, lymphocytic, neurogenic) and etiology. The most common cause of cough in children is viral infection producing “normal cough”. A cough lasting more than 4-8 weeks or “chronic cough”, must be carefully evaluated in order to rule out specific causes that may include the entire pediatric pulmonology spectrum and also extrapulmonary disorders.

Chronic cough can be challenging for the family and the pediatrician due to its broad differential diagnosis. If the cough persists for more than 4 weeks, a thorough reassessment of the anamnestic data is required, a complete clinical examination to which specific complementary investigations will

be performed. Children with chronic cough should be managed with pediatric-specific algorithms because those who are treated in this manner have improved clinical outcomes. The causes of specific chronic cough can be categorized in the following groups: aspiration, asthma and allergies, airway abnormalities, infections (chronic or less common), protracted bacterial bronchitis, chronic suppurative lung disease and bronchiectasis, interstitial lung disease, airway irritants (chemical or physical) and extrapulmonary causes. Recent studies have focused on protracted bacterial bronchitis as a major cause of chronic cough in pre-school children and its role as a possible precursor of bronchiectasis.

The management of a chronic, non-specific cough in children remains a challenge as it requires careful consideration and long-term follow-up and the treatment options remain limited. An empirical trial of inhaled corticosteroids can be considered in children with a troublesome non-productive chronic cough, but if there is no clear response to the medication after two to four weeks, it should be stopped. For children who develop a wet, productive cough, a trial of antibiotics for two weeks can be offered. These families and children require support and very careful follow-up. Those who respond poorly are best managed in experienced referral centers early in the course of their illness.

LECT 28

BRONCHIOLITIS TODAY

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INTRODUCTION

Acute bronchiolitis is a viral infection of the lower respiratory tract and represents one of the most substantial health burdens for infants and young children worldwide. Clinically patients first present symptoms of viral upper respiratory infection while lower respiratory tract symptoms including a persistent cough, tachypnea, and increased work of breathing follow later; in some cases, the bronchiolitis may progress to severe hypoxemia and cyanosis.

Respiratory syncytial virus (RSV) is the most prevalent viral cause of bronchiolitis in infants. Some evidence suggests that co-infections, particularly RSV with rhinovirus (RV), which represents the combination most commonly reported, or with

metapneumovirus, could be associated with a more severe disease course compared with infection by a single virus.

Among children suffering from severe bronchiolitis, different clusters of patients can be identified: patients with RSV-induced bronchiolitis characterized by younger age and mechanical airway obstruction due to mucus and cell debris. This condition increases the risk of recurrent wheezing and, mildly, of asthma. Infants with RV-induced wheezing, associated with an atopic predisposition, are at high risk to develop asthma, especially in patients with a clinically severe first episode. Finally, episodes of wheezing due to other viruses, like bocavirus and metapneumovirus, probably less severe and at lower risk to cause long-term sequelae.

TREATMENT

Substantial knowledge gaps and controversies exist in the management of acute bronchiolitis. Most guidelines recommend only supportive treatment, such as oxygen, nasal suctioning, mechanical ventilation, and hydration. High flow oxygen therapy using nasal cannulae has shown promising results. There are conflicting data across clinical guidelines about the role of nebulized hypertonic saline in the acute management of bronchiolitis. In outpatients, oxygen saturation, admission to hospital, or time to resolution of symptoms did not improve with bronchodilator usage compared with placebo. Therefore, guidelines do not recommend treatment with bronchodilators for bronchiolitis. Guidelines recommend the use of corticosteroids for infants with bronchiolitis. No benefit for epinephrine compared with placebo for inpatients in-hospital length of stay or other outcomes.

Evidence suggests the efficacy of immunoprophylaxis with palivizumab, a humanized monoclonal antibody against the RSV F glycoprotein in the management of bronchiolitis. This treatment was able to decrease the risk of hospitalization due to severe RSV illness among preterm infants (72% reduction), among those with chronic lung disease (65% reduction), and with hemodynamically significant congenital heart disease (53% reduction). Interestingly, palivizumab effectively reduced recurrent wheezing episodes following hospitalization due to RSV, but not asthma. Regarding new therapies, there are currently many RSV vaccines and antibodies in preclinical development and several others in clinical development. New molecules have been identified for the treatment of RSV infection and are currently in (advanced) preclinical or clinical development.

CONCLUSIONS

Further research is required in order to direct focus to more personalized management plans in the treatment of acute bronchiolitis. Viral etiology should be used since differentiating the causal agent of the first episode of severe bronchiolitis appears to be a critical factor. This could be an opportunity for designing secondary prevention strategies for asthma since different patient groups are likely to respond to different treatments.

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LECT 29

THE CHILD WITH SEVERE ASTHMA: INFECTIONS AND MORE

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Asthma is a chronic inflammatory disease of the airways, which is characterized by reversible airflow obstruction, airway hyper-responsiveness, airway remodeling, and gradual deterioration of lung function. Severe asthma is a complex disease presenting with a variety of different multiple clinical phenotypes with a number of undergoing pathophysiologic mechanisms which cause the clinical expression of the disease and may represent potential targets for therapy and prognostic factors. The vast majority of children with asthma usually reach a satisfactory control of symptoms with a medium-low dose of inhaled corticosteroids (ICSs), but approximately 5% has a condition of severe asthma. Within this group a distinction must be considered between patients with severe asthma not responding to medical treatment and patients with "difficult to treat" asthma, characterized by

an inadequate control of symptoms due to the presence of misleading factors such as uncorrected diagnosis, comorbidity or environmental factors, lack of adherence to the treatment and psychological factors [1].

In clinical practice, the first necessary step for management is to confirm the diagnosis of asthma. The diagnostic confirmation is reached through careful adherence to a well-defined diagnostic path and after a specialized evaluation of at least three months. At the end of this process, it is possible to define severe asthma and to ideally identify the specific endotype and the biomarkers allowing to recognize the sensitive patients to biological agents. A correct selection of suitable patients is mandatory both for medical reasons and for the high cost of biological agents.

In children, asthma is mostly characterized by a TH2-mediated inflammatory response with the release of IL-4 and IL-13 and production of IgE and IL-5, leading to eosinophils survival.

The use of a biological agent has to be considered when there is no control of the symptoms, despite all the measures indicated by the guidelines: control of the environment and strict adhesion to drug therapy, as it is indicated by GINA guidelines [2]. This condition is verified at level 4 GINA guidelines with the use of high-doses ICSs associated with LABA and other controllers such as leukotrienes antagonists.

The main advantage of treatment with biological agents is that they have selective actions towards specific points in the inflammatory cascade that develops in asthmatics and different agents target different endotypes of disease. Therefore, these agents, which allow addressing a specific therapeutic intervention, may represent a major therapeutic option for the next future in children with severe asthma.

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LECT 30

RESPIRATORY INFECTIONS IN THE FIRST YEAR OF LIFE AND DEVELOPMENT OF CHRONIC LUNG DISEASES

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Growing evidence has shown that chronic obstructive respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD) have their roots in the womb. Together with a genetic predisposition, early respiratory infections, especially respiratory syncytial virus (RSV) and rhinovirus (HRV) play a pivotal role in later respiratory health and can influence unfavorable lung function trajectories. RSV is a major worldwide cause of morbidity and mortality in children under five years of age, and it is involved in asthma inception. Among infants with RSV bronchiolitis, the estimated risk of later developing recurrent wheezing and asthma is 30-40%. RSV vaccine, antivirals, and new monoclonal antibodies are currently being investigated. Also, recurrent respiratory infections and pneumonia in the first years of life are co-factors in the development of chronic lung disorders and are associated with impaired lung function.

There is an urgent need for early biomarkers to identify risk profiles predictive of chronic respiratory conditions; the "omic" technologies are promising in this regard. Avoidance and prevention of respiratory tract infections in the first years of life may help to prevent chronic lung diseases.

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LECT 31

NUTRITION IN PEDIATRICS: PREVENTION OF NONCOMMUNICABLE DISEASES

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Nutrition and dietary patterns are recognized as modifiable risk factors able to influence respiratory disease development and progression as they can regulate the immune system. Therefore, nutrients can have a high impact on individual respiratory health and contribute to the development of the organism, and should not be considered only as an energy source. Prenatal and early postnatal periods have a critical role in the individual outcome, as Barker affirmed: "Much of human development is completed during the first 1,000 days after conception". The first 1,000 days of life from conception to two years are considered critical in nutrition for enhancing short and long-term health outcomes. Early nutrition may influence the risk of developing noncommunicable diseases (NCDs) later in life, including heart disease, hypertension, type 2 diabetes (T2DM) and chronic respiratory diseases (such as asthma) through epigenetic mechanisms. Mediterranean Diet represents the cornerstone of a correct dietary pattern for the pregnant and breastfeeding woman and the children, particularly for the prevention of NCDs.

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LECT 32

OVERVIEW ON CHRONIC NEONATAL DIARRHEA

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Diarrhea is common in infants (children less than 2 years of age), usually acute, and, if chronic, commonly caused by allergies and occasionally by infectious agents. Less commonly anatomical causes as short bowel syndrome acquired or congenital must be excluded. Congenital diarrheas and enteropathies are rare causes of chronic diarrhea in infants. Evaluation is a long and difficult process and infrequently leads to a definite diagnosis. However, genomic analyses and the development

of model systems have increased our understanding of pathogenesis. With these advances, a new diagnostic approach is needed. We propose a revised approach to determine causes of chronic diarrhea in infants, based on stool analysis, histologic features, responses to dietary modifications, and genetic tests. After exclusion of common causes of diarrhea in infants, the evaluation proceeds through analyses of stool characteristics (watery, fatty, or bloody) and histologic features, such as the villus to crypt ratio in intestinal biopsies. Infants with chronic diarrhea resulting from defects in digestion, absorption, transport of nutrients and electrolytes, or neuroenteroendocrine cell development or function have normal villi to crypt ratios; defects in enterocyte structure or immune-mediated conditions result in an abnormal villus to crypt ratios and morphology. Whole-exome and genome sequencing in the early stages of evaluation can reduce the time required for a definitive diagnosis, or lead to the identification of new variants associated with these enteropathies. Characterization and investigation of new chronic diarrhea disorders will improve the management of patients and advance our understanding of epithelial cells and other cells in the intestinal mucosa.

LECT 33

PROBIOTICS IN PEDIATRICS: WHERE WE ARE HEADING

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The importance of the gut microbiota at the early stage of life and its longitudinal effect on host health has recently been well documented. The microbiota in the first period of life is complex and related to the kind of delivery, kind and of feeding (human milk versus artificial milk formulas) and to other factors such as antibiotics. Currently, our understanding of the underlying molecular pathophysiology of such ambient is not well understood, although it is well appreciated that the probiotics play a key role in some conditions such as colicky, atopic disorders, necrotizing enterocolitis, diarrhea, virus infection and antibiotic-associated diarrhea. Over the past decade, it has become clear that the host intestinal microbiota can modify behaviors relevant to stress responses and to regulate immune, gastrointestinal

system molecular changes at a transcriptional level. In fact, recently the intestinal microbiota, its influence on the developing immune system and the mechanisms by which probiotic microbes can modify host-microbe interactions are the issues of active investigations.

Some probiotic strains have strong anti-inflammatory effects, e.g., through modifications of toll-like receptors or NFκB signaling and changes in the cytokines, and decrease intestinal permeability through establishment the mucus layer and tight junctions. Probiotics also can influence energy ingathering from ingested foods and impact growth and the intestinal mucosa through the release of partially degraded human milk oligosaccharides, short-chain fatty acids, amino acids, and vitamins. Further probiotics can change the composition of the intestinal microbiota by outcompeting other microbes and by producing biofilms or bacteriocins. An innovative study of different mechanisms and probiotic microbes has the potential to better clarify the dysbiosis-associated disease courses. Despite a recent large RCT published in 2018 in *NEJM* reported no effect of *L. rhamnosus GG*, current evidence shows that, overall, *L. rhamnosus GG* reduced both the duration of diarrhea and hospitalization in inpatients. However, huge of the available data is from animal or *in-vitro* work and human studies of adults or older children. The evidence for the benefit of probiotics in infantile colic is strong but limited to the *L. reuteri DSM 17938* strain and breast-fed infants. Recently, we have shown that probiotics can improve colicky symptoms and influence Treg in breastfed infants treated with *L. reuteri DSM 17938*.

The complex interactions between host immune function and probiotics make further investigation of mechanisms in the newborn host essential for understanding this biologically inimitable group of subjects. Manipulating the timing of colonization in infants further supports the importance that the microbiome has during early time windows that are crucial for establishing normal responses to the treatment with probiotics in these infants.

Despite the availability of evidence, the decision for a neonatologist to initiate routine probiotic supplementation to preterm infants continues to be undefined. It remains unclear whether probiotic species colonizes in the gut over the long term from early infancy. Lastly, although the short-term modulatory impact of probiotics on gut microbiota has been shown in several studies, no studies

focused on longer time consumption of probiotics have been published.

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LECT 34

PEDIATRIC GASTROESOPHAGEAL REFLUX CLINICAL PRACTICE GUIDELINES

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This is an update of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2009 clinical guidelines for the diagnosis and management of gastroesophageal reflux disease (GERD) in infants and children and is intended to be applied in daily practice and as a basis for clinical trials.

There some differences from the 2009 guidelines:

1. it focuses on reducing acid suppression whenever possible with short empiric trials of 4-8 weeks recommended for GERD symptoms;
2. it shifts away from attributing respiratory and laryngeal symptoms to GERD;
3. it adds an algorithm for typical symptoms to incorporate reflux testing to characterize patients further to differentiate patients with reflux based diagnoses versus functional diagnoses;
4. it adds a recommendation for change of formula to a protein hydrolysate or amino acid-based formula before acid suppression in infants.

For diagnostic approach:

1. the onset of GERD symptoms after the age of 6 months or persistence of symptoms beyond 12 months raises the possibility of alternative diagnoses to infant GERD;
2. referral to a pediatric gastroenterologist for evaluation to diagnose possible GERD and to rule out other diagnoses is recommended;

3. the goal of additional testing is to rule out mimickers or complications of GERD;
4. testing may include laboratory tests, contrast imaging, upper GI;
5. endoscopy and/or esophageal pH/MII, depending on presenting symptoms.

The new recommendations regarding diagnostic interventions include:

1. barium contrast studies and ultrasound should be used to exclude anatomical abnormalities not to diagnose GERD in infants and children;
2. esophago-gastro-duodenoscopy with biopsies should be used to assess complications of GERD (in case an underlying mucosal disease is suspected and before the escalation of therapy) and not to diagnose GERD in infants and children;
3. salivary pepsin should not be used for the diagnosis of GERD in infants and children;
4. the currently available extra-esophageal biomarkers should not be used for the diagnosis of GERD in infants and children;
5. barium contrast studies and ultrasound should be used to exclude anatomical abnormalities not to diagnose GERD in infants and children;
6. esophago-gastro-duodenoscopy with biopsies should be used to assess complications of GERD (in case an underlying mucosal disease is suspected and before the escalation of therapy) and not to diagnose GERD in infants and children;
7. salivary pepsin should not be used for the diagnosis of GERD in infants and children;
8. the currently available extra-esophageal biomarkers should not be used for the diagnosis of GERD in infants and children.

LECT 35

SYRIANS, PALESTINIANS AND IRAQI REFUGEES IN LEBANON

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INTRODUCTION

In February 2011, the 'Arab Spring' begun in Syria. The conflict between protestors and government forces in Syria has developed into a complex crisis involving many parties and led to a unique humanitarian disaster. As the years are passing, the

situation of the civilians in Syria, along with the Syrian refugees, is getting worse. Lebanon, despite its small size, is hosting over 1.3 million refugees from Syria, equal to more than 20% of Lebanon's original population (UNHCR data portal 9th June 2014). Not less than 20 million people in Syria need humanitarian help; in addition, 4.1 million coasted over the border as refugees in neighboring countries. These are becoming a big burden on welcoming countries. Almost 1.3 million registered Syrians evacuated their country and established in Lebanon, where in conjunction with Palestinian refugees they now make up more than a quarter of the population.

FIGURES AND FACTS OF SYRIAN REFUGEES

Refugees fleeing Syria continue to enter Lebanon daily. Lebanon has experienced a massive influx of refugees the past 5 years, including 1.3 million people escaping from the conflict in Syria. This represents almost 1 in every 5 people in Lebanon. This increased population has a dramatic impact on the country's social, economic aspects, along with the local infrastructure that is deteriorating rapidly. Half of these refugees are children. There are 2 kinds of disasters: 1) Nature made disasters (for example, the tsunami in Indonesia or the tornado in New Orleans); 2) Man-made disasters: war. This year there are 68.5 million refugees, the biggest number since world war 2. Two third of the refugees come from 6 countries: Syria, Myanmar, Afghanistan, Somalia, Iraq, and Sudan. Palestinians is the largest and more protracted refugees' crisis since 1948.

REGISTRATION

Despite the efforts of these N.G.O.s, around 30,000 Syrians born as refugees in Lebanon are not registered with any government leaving them in statelessness and depriving them of their basic rights such as going to school, having a job or even getting married. The United Nations refugee agency estimated that around 70% of infants born in Lebanon to Syrian refugees are off the books mostly due to the unavailability of their parents' marriage license. Therefore, acquiring legal documentation by the Lebanese authorities for Syrian newborns refugees is a major concern. The U.N. refugee agency and the N.G.O.s have been raising awareness among Syrian refugees across the Middle East to register their children; especially in Lebanon were the highest number of non-registered newborn is detected, in contrast to Jordan were 70% of children born to Syrian refugees are registered due to facilities in the process and lesser phases then those in Lebanon.

COST OF HOSPITALIZATION

If refugees are registered at UNHCR, they are allowed to be hospitalized in certain circumstances, mainly in NICU and PICU for a short stay with a top cost that cannot be over headed. UNHCR pays 90% of the bill at reduced prices, and the rest 10% should be paid by the refugees. Many times, health practitioners have heard desperate refugee's parents saying: "We cannot pay, give us the baby, and we will let him dye". Other more difficult words to hear are: "Alright let him dye, and we will bring another child".

PROSTITUTION

Almost every day we read in the newspapers about Syrians minors and adolescent being obliged to work as a prostitute, and they are obliged to do such jobs to assure earnings and protection for their families being protected by Syrians protectors.

SYRIANS IN JAIL IN LEBANON

A recent publication by Lebanese President has revealed that around 40% of prisoners in Lebanese jails are Syrians.

CHILDREN KILLED IN SYRIA

More than 10,000 children have been killed in the Syrian civil war, the United Nations says, while many more are subjected to "unspeakable" suffering, including rape, torture, and recruitment for combat.

PALESTINIANS REFUGEES

After Yarmouk camp battle near Damascus, 42,000 Palestinians refugees from Damascus arrived in Lebanon adding to the 450,000 Palestinians already refugees in Lebanon. Sixteen thousand arrived in one week.

WAR IN IRAQ

According to the Iraqi Red Cross, more than 33% of disabled children are victims of war and bad treatments. UNICEF in Iraq said that it needs 42 million dollars only to give water and food for Iraqi children.

WHAT IS BIRTH AND BEYOND ASSAMEH?

With a group of volunteers, civilians and pediatricians, an N.G.O. named "BIRTH AND BEYOND – ASSAMEH" was created. The purpose is to create a pediatric department with all the facilities and a very well equipment that may receive sick patients from poor economic conditions whether Lebanese, Syrians, Palestinians or undetermined nationality that are usually Syrians born in Lebanon but whom Syrian regime denies the right of nationality for several reasons. Knowing that in Lebanon, the rate of birth is around 60,000 newborns per year, we have 750,000 newborns in Lebanon which are Syrians refugees, and most of

them are not registered to Syrian authorities and have an undetermined nationality.

Carlos Slim Pediatric Center: It is the Pediatric Department at Quarantina Governmental Hospital equipped by BIRTH AND BEYOND – ASSAMEH. Equipment includes: a Neonatal Intermediate Care Unit of 16 incubators, a Pediatric Intensive Care Unit of 4 beds, a Pediatric Department of 12 beds, an OutPatient Department with a vaccination program. There is an increasing number of patients admitted: 520 patients in 2016, 750 in 2017, 900 in 2018, and probably 1,000 in 2019. Twenty-seven patients did not have official papers and nationality, 6 newborns were found in the garbages, 2 children suffered from physical abuse and battered child syndrome. In one case, the parents were trying to sell their child.

Pathologies we are not used to seeing anymore include: organo-phosphate intoxication, malformation syndromes, metabolic diseases due to consanguinity, snakes bites, severe dehydration, severe sepsis, severe meningoencephalitis.

LECT 36

GUT MICROBIOTA AS A TARGET FOR PREVENTION AND TREATMENT OF FOOD ALLERGY

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The gut microbiota plays a pivotal role in immune system development and function. Modification in the gut microbiota composition (dysbiosis) early in life is a critical factor affecting the development of food allergy. Many environmental factors, including cesarean delivery, lack of breast milk, drugs, antiseptic agents, and a low-fiber/high-fat diet can induce gut microbiota dysbiosis and have been associated with the occurrence of food allergy. New technologies and experimental tools have provided information regarding the importance of select bacteria on immune tolerance mechanisms. Short-chain fatty acids are crucial metabolic products of gut microbiota responsible for many protective effects against food allergy. These compounds are involved in epigenetic regulation of the immune system. These evidences provide a foundation for developing innovative strategies to prevent and treat food allergy.

LECT 37

PRECISION NUTRITION IN PEDIATRICS

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Recent studies have demonstrated that nutrition has an impact on long-term health and lifespan, highlighting that proper nutrition may reduce the prevalence of non-communicable chronic diseases and lead to healthier individuals with longer life expectancy [1]. In this setting, early-life nutrition has a crucial role in affecting mid-term and long-term metabolic and nutritional outcomes [1]. However, the mechanisms underlying the effects of early nutrition on health are yet to be fully understood. Recently, a plethora of evidence accumulates demonstrating that alterations in intestinal microbiota and modulation of the immune response induced by food serve as main mechanisms involved in the development of inflammatory conditions such as asthma, inflammatory bowel diseases, and cardiovascular disease. The Mediterranean diet (MD), traditionally practiced in countries of the Mediterranean basin especially Greece, Italy, and Spain is considered a prototypically healthful dietary pattern, associated with longevity and lower incidence of several chronic non-communicable diseases sharing some modifiable behavioral risk factors [2]. MD is enriched with fish, monounsaturated fats from olive oil, fruits, vegetables, whole grains, legumes/nuts, and moderate alcohol consumption [2]. The particular combination of nutrients typical for the MD, associated with the limited use of simple carbohydrates, is increasingly suggested as a preferred diet for human health [2]. Indeed, it has been shown to reduce the risk of cardiovascular disease, cancer, depression, colorectal cancer, diabetes, obesity, asthma, cognitive decline, and premature death in general [2]. In particular, some studies reported a positive effect of the MD on glycemic control. However, whether this diet will "fit all" or some individuals will benefit, and some not is unknown. Recently, Zeevi et al. developed an algorithm enabling to predict the personalized postprandial glucose responses to food in adult healthy individuals [3]. The rationale of the study called "Personalized Nutrition Project" was based on the hypothesis that universal dietary recommendations may not suit all individuals'

needs and that individuals may respond differently to the same food, and the individual response could be predicted based on repeated exposures and observation of the glucose blood level response and the gut microbiome [3]. The authors built a model on which predictions were based on hundreds of personalized features, including clinical, background and dietary data, blood tests, personal lifestyle measures, and gut microbiome data. Once developed, these complex algorithms were shown to accurately predict the glycemic response. This trial clearly demonstrated that adult patients treated with a personalized algorithm-based diet were able to significantly lower their postprandial glucose responses [3]. Personalized nutrition has never been tested in children to date.

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LECT 38

FEW RULES FOR PEDIATRIC NUTRITION

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Chronic non-communicable diseases (NCDs), such as those related to overweight and obesity, represent major health issues worldwide. It is commonly accepted that early intervention in the pediatric age, or even earlier, during pregnancy, has a positive impact in reducing life-course risk of NCDs. Some few, useful rules in pediatric nutrition are important for a healthy life. Breastfeeding, as recommended by World Health Organization (WHO), should be exclusive in the first 6 months of life and should be continued during the complementary feeding period, until 12 months, or even afterward. Complementary feeding should not be started before the completed

fourth month of age. Energetically adequate foods should be introduced, paying attention to limit the protein intake and to favor the intake of iron-rich foods. High protein intakes in early life has been associated with a later increased risk of overweight and obesity. Intake of simple sugars, above all those from snacks and sugar-added beverages, should be limited or preferably avoided at all. Similarly, polyunsaturated fatty acids (PUFAs) should be preferred in the diet of infants and children: quality of the ingested fats is more important than their quantity in a healthy diet. Other favorable eating habits include limiting sodium intake and consuming breakfast regularly.

LECT 39

RECURRENT WHEEZING AND GASTRO-ESOPHAGEAL REFLUX IN CHILDREN – 5 YEAR REPORT

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BACKGROUND AND AIMS

The association of gastroesophageal reflux with recurrent wheezing is suggested by different studies. This study aims to explore this relationship and to evaluate the outcome after appropriate treatment.

METHODS

A group of 85 children with recurrent wheezing, admitted in a pediatric gastroenterology regional center in Northeast Romania, were evaluated for the presence of gastroesophageal reflux by 24-hour continuous esophageal pH monitoring and the results were interpreted using the Boix Ochoa score. All patients with positive score received treatment with proton pump inhibitors, and they were re-evaluated after 2 months.

RESULTS

71 children (83.53%) had gastroesophageal reflux proved by a positive Boix Ochoa score, while 14 (16.47%) had a negative score, with statistical significance ($\chi^2 = 6.88$, $p = 0.0086$, 95% CI). After a 2 months treatment with proton pump inhibitors, the Boix Ochoa score remained positive for 15 patients (21.13%).

CONCLUSIONS

Recurrent wheezing is a solid reason for evaluating the presence of gastroesophageal reflux by 24-hour continuous esophageal pH-metry. The bronchial

spasm triggered and maintained by the aspiration of the acid refluxate remains the most plausible explanation of this relationship and association. Adequate treatment of gastroesophageal reflux also solves the recurrent wheezing.

LECT 40

GASTROINTESTINAL INVOLVEMENT IN AUTISTIC CHILDREN: THE METABOLOMICS LESSON

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INTRODUCTION

New insights suggest that the aggressive behavior of autistic patients might be related to the presence of certain bacteria or microbial imbalance, the so-called dysbiosis. The presence of this latter can be identified through metabolomics. Metabolomics allows the identification of the whole sets of circulating small molecules produced by eukaryotic and prokaryotic cells [1]. Metabolites can play a causative role in psychiatric disorders by passing into the brain through the blood-brain barrier, causing either modulation of behavior and peripheral inflammation [2]. In particular, the presence of tryptophan and its by-product kynurenine have potent neuropsychiatric effects [3]. The purpose of our study is to investigate the presence of these two metabolites in a cohort of autistic patients which are eventually compared to healthy controls' subjects.

MATERIALS AND METHODS

99 subjects (57 toddlers and 42 adolescents) were enrolled in the study: 52 autistic spectrum disorder (ASD) patients, and 47 healthy controls. Parents of both ASD children and healthy controls gave written informed consent before the inclusion in the study. ASD patients were recruited at the Children Psychiatry Unit of the University Hospital of Rome Tor Vergata (Italy) and the Pediatric Division of University of Bari (Italy). Exclusion criteria for

ASD included genetic syndromes, neurological disorders, ongoing acute diseases and known inborn errors of metabolism.

RESULTS

Urine samples collected from both ASD and healthy controls cohorts were analyzed and compared through GC-MS and multivariate statistical analysis. 99 samples (31 ASD cases and 26 controls and 21 ASD cases and 21 controls) underwent OPLS-DA analysis. Among the detected metabolites belonging to ASD patients, tryptophan, and kynurenine were identified.

CONCLUSION

Recent advances highlight the potential mechanisms, involving bacterially-derived metabolites through which brain behavior and immunoregulation are influenced.

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LECT 41

NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY; GOLDEN HOUR

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Neonatal hypoxic-ischemic encephalopathy (HIE) represents one of the major causes of neonatal mortality and neurological morbidity occurring in 3-5 out of 1,000 live births. Therapeutic hypothermia (TH) has been used to treat newborns with severe and moderate HIE and currently is considered the goal treatment for HIE.

The etiology is caused by the dyad hypoxia-ischemia and secondarily the failure of cerebral perfusion to the fetus before or during delivery. For this reason, it is very important to recognize early hypothetical cases of HIE. The HIE diagnosis is insidious, in some cases, particularly during the first 6 hours of life.

HIE is a central nervous system (CNS) disorder mainly characterized by alterations in mental status, hypotonia, seizures, feeding, and respiration abnormalities. Unfortunately, these signs and symptoms could not appear at the same time. For this reason, Sarnat modifies classification with the following findings such as level of consciousness, muscle tone, posture, tendon reflexes, myoclonus, Moro reflex, pupillae, seizures, and EEG picture has been proposed. Recently some Authors have evaluated infants with mild HIE in the first 6 hours, with early neurologic examination findings establishing that a total Sarnat score of ≥ 5 when performed at < 6 hours of age could detect future disability.

The principal crucial point is considered the suspicious of HIE during the first hours according to the metabolic and neurological clinical parameters. We have considered in this focus clinical cases that do not fully meet the “classical” diagnostic criteria and particularly those with a cord blood gas pH above 7 and base excess (BE) between -12 and -16 and those whose neurological signs have not clearly appeared. The neonatologist at first instance, when HIE is suspected, should have caution and collect all the evidence to show that the baby has been exposed to hypoxia from severe to mild. Chalak showed that out of 63 newborns with mild HIE untreated with TH disability occurred in 16% of infants at 18-22 months opening a new road for patients with ambiguous HIE between mild and moderate.

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LECT 42

HYPOXIC ISCHEMIC ENCEPHALOPATHY: MANAGEMENT FROM DELIVERY ROOM TO NEONATAL INTENSIVE CARE UNIT – “IDEAL TIMING FOR IDEAL BRAIN PROTECTION”

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Perinatal hypoxia-ischemia remains to date the primary cause of neonatal brain injury, leading to a high mortality rate and long-term neurological disabilities. Its pathogenesis is complex with a multitude of pathways of the inflammatory cascade that contribute to central nervous system cellular dysfunction. As oxidative injury plays a crucial role in the pathogenesis and progression of hypoxic/ischemic brain damage, it is clear that the inhibition of this free radical generation could represent a potential mechanism for counteracting this condition. Hypothermia is the safest method to prevent morbidity and mortality in asphyxiated newborns. However, to date, new supportive options are needed to enhance the neuroprotective effects of the hypothermia, which should aim to reduce the production of free radicals and to have anti-inflammatory and anti-apoptotic actions. In this context, in recent years, melatonin has revealed a promising drug for various acute and chronic diseases. Its efficacy, low toxicity, and ready cross through the blood-brain barrier, making it a promising neuroprotective molecule.

LECT 43

NEONATAL CARDIAC EMERGENCIES

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The main conditions potentially leading to clinical emergencies in pediatric cardiology, especially in the neonatal period, are:

1. congenital heart diseases (CHD);
 2. the persistence of fetal circulation;
 3. transient myocardial ischemia;
 4. arrhythmias.
1. CHD are the most common congenital disorders in fetuses and newborns, with a reported prevalence of 20:1,000 and 10:1,000, respectively. In neonatal cardiac emergencies, usually represented by ductal-dependent CHD, a patent ductus arteriosus (PDA) is required to sustain pulmonary or systemic circulation and to allow adequate mixing between parallel circulations. In critical right heart obstructive lesions, a condition of PDA is necessary to supply blood flow to the lungs. These are represented by pulmonary stenosis, pulmonary atresia with the intact

ventricular septum (PAIVS), or associated with inter-ventricular defect (IVD), and Tetralogy of Fallot. In critical left heart lesions, such as aortic stenosis/coarctation and left heart hypoplasia, PDA supplies systemic circulation. In conditions characterized by parallel circulations, such as great arteries transposition (TGA), a bidirectional flow through PDA allows mixing between oxygenated and deoxygenated circuits. Clinical associated features may vary from cyanosis to heart failure symptoms, depending on the specific CHD. Due to the high risk of morbidity and mortality, neonates affected by ductal-dependent CHD should be treated with prostaglandin E1 (PG-E1) to re-open or maintain a PDA (therapeutic range 0.02-0.2 mcg/kg/min); this, together with a rapid transfer to a tertiary center, represent imperative measures to guarantee the highest level of care.

2. The persistence of fetal circulation, a condition affecting about 1:1,500 newborns, is characterized by the presence of pulmonary arterial hypertension and lacking closure of ductus arteriosus and oval foramen, with the persistence of a right > left shunt through these structures.
3. Transient myocardial ischemia is usually secondary to asphyxia or hypoglycemia. Color Doppler Echocardiography allows the exclusion of a congenital malformation and can detect marked ventricular myocardium hypokinesia.
4. Another cause of heart failure, therefore representing a neonatal emergency, is paroxysmal supraventricular tachycardia. This condition, showing an incidence of 1:10,000 newborns, is more common in neonates without structural heart disease. The appropriate treatment strictly depends on the clinical presentation. In the case of heart failure or cardiogenic shock, the therapy of choice is adenosine triphosphate (ATP), eventually followed by electrical cardioversion. Contrarily, if paroxysmal supraventricular tachycardia is well-tolerated, vagal maneuvers can be applied. Since this condition can recur, especially in neonates, anti-arrhythmic prophylaxis is required to restore the sinus rhythm.

LECT 44

STABILIZATION AND TRANSPORT OF NEWBORNS WITH CARDIAC DISEASE

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Congenital heart diseases (CHD) have an incidence that varies from 0.6% to 1% of all live-born neonates. Around a third of defects is potentially fatal during the neonatal period. The survival of the majority of these critical newborns has been made possible thanks to the progress in diagnosis, intensive care, surgical techniques, and post-surgery management. Many newborns with CHD will be born in a not third-level center or in a center in which the pediatric cardiologist is not present. They may have a known or an unknown cardiac defect or an evolving cardiac disease. Sometimes it can be very complicated to identify and diagnose cardiac disease in these newborns due to the complex physiopathology and the aspecificity of the clinical findings, so much that some clinical pictures are misdiagnosed as sepsis or respiratory failure. It is of fundamental importance that a neonate that shows shock, respiratory distress, acidosis, or cyanosis due to a cardiac cause is promptly identified and stabilized from both a respiratory and hemodynamic point of view.

The respiratory stabilization aims to guarantee adequate ventilation; it could require the necessity of ventilatory support (invasive or not invasive) and the oxygen administration that must always be carefully regulated in order to maintain the arterial oxygen saturation (SaO₂) between 80% and 85%.

The hemodynamic stabilization needs the positioning of vascular access, better if it is central (venous or arterial umbilical catheter) for the infusion of drugs and fluids, for the correction of the metabolic acidosis and monitoring of blood pressure. The administered drugs are prostaglandin (PGE1), inotropic, diuretic, and sodium bicarbonate. PGE1 should be started in the suspect of the ductal dependent defect to maintain the patency of the ductus arteriosus (or to re-open it if closed or narrowed). The inotropic infusion should be initiated to ameliorate the myocardial contractility and the perfusion of vital organs and peripheral tissues. Among the most administered inotropic drugs, there are the vasoactive amines: dopamine and dobutamine. Others inotropic agents are isoproterenol, epinephrine, and milrinone. The most administered diuretic is the furosemide. The use of sodium bicarbonate may help in the correction of the metabolic acidosis due to anaerobic metabolism and responsible, in its severe forms, of the reduced myocardial function, of the pulmonary vasoconstriction and the inefficacy of the inotropic drugs.

After the initial stabilization, the newborn must be transferred to a third level center. The primary aim of every transport system is to provide a safe, timely, and controlled transfer. Special considerations should be given to vascular access, airways stability, and O₂ therapy during the transport.

It is never enough to highlight that proper transport requires an accurate and completed information exchange from the team of the sending hospital to the accepting hospital.

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LECT 45

INTERVENTIONAL PROCEDURE IN NEWBORNS

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With increased experience with interventional cardiac procedures and improved equipment and techniques, some of the most frequent Congenital Heart Disease can be treated in the cath lab also in newborns. It has evolved from atrial septostomy in the 1970s to a wide range of procedures including device closure of various defects and percutaneous valve implantation nowadays. The most recent procedure that is becoming available also in preterm infants is the PDA closure. Traditionally, surgical ligation has been used to provide definitive ductal closure, but surgery has risks; drug therapy is effective in medically closing the ductus in some infants, but side effects have led to growing uncertainty on the use of drug therapy. Recent studies suggest a growing interest, and use of catheter-based PDA occlusion among lower weight infants (< 6 kg), but neonatal medicine is replete with examples of promising interventions that did not translate into a long-term benefit, including some that caused harm. While catheter-based PDA closure has the potential to provide a safer alternative

than surgical ligation to achieve ductal closure, conclusions on the optimal treatment among lower weight infants with a persistent ductus remain unanswered. At the moment we know that based PDA closure is feasible, but lack of standardized entry criteria, data collection, definitions, limits interpretation. Pragmatic clinical studies comparing catheter-based closure versus alternative treatments (surgical ligations, conservative treatment) appropriately powered to detect potential differences in long-term, clinically relevant outcomes are needed to generate relevant and generalizable data. This goal is achievable but will require interdisciplinary (neonatology, cardiology) and multi-center collaboration.

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LECT 46

THE NEONATAL ECG: HOW TO APPROACH THE ECG OF THE NEWBORN AND WHAT TO BE ABLE TO IDENTIFY FROM IT

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The neonatal electrocardiogram (ECG) is an important diagnostic not-invasive tool even if its utilization is reduced due to the spreading of echocardiography. Despite this, neonatal ECG still gives important information about the neonatal heart both as a snapshot and by serial data when the tracings are repeated in time. The ECG is part of the monitoring in neonatal post-resuscitation care and of a thorough approach to neonates presenting with respiratory distress and/or cyanosis. Furthermore, ECG can help evaluate a newborn with the suspicion of congenital heart disease (CHD) without a fetal diagnosis.

The description of an ECG is "alphabetical": P wave; PR segment; QRS complex; ST-segment; T wave; QT interval.

The P wave illustrates the origin of the electric stimuli, usually from the right atrium. Thus, it is positive in II and negative in aVR. Conditions causing atrium dilatation, atrium hypoplasia,

ectopic origin of the electric stimuli modify the morphology of the P wave. The latter is absent in junctional rhythms.

PR segment. It represents the progression of the stimulus to the ventricles; it is physiologically short in the neonate and even shorter in sustained tachycardias. Vice versa, it is prolonged in AV block (maternal immunologic disease, atrioventricular canal, Ebstein anomaly, congenitally corrected transposition of the great arteries).

The QRS represents the electrical systole with the right ventricle (RV) more evident ("R" V1-V3 and "S" V5-V6) than the left ventricle (LV) in newborns. Pathologic aspects alter this ratio showing "low" RV potentials in CHDs with RV hypoplasia and "low" LV potentials in CHDs with LV hypoplasia. Eventually, ventricular potentials higher than expected, either right or left, will advise a CHD with a fixed obstruction to the ventricular outflow right or left respectively.

The ST tract and the T wave depict repolarization. Physiologically the ST waveform should be isoelectric, but slight deviations (2 mm) up or down are normal in newborns. The T wave is positive in V1-V3 during the first days of life pooling the QRS in drawing the RV mass prevalence. After delivery room resuscitation, it is frequent to find deviations of the ST associated with anomalies of the T wave drawing an ischemic pattern [1]. In most cases, these aspects of post-resuscitation are benign and self-limiting.

The QT interval combines systole and repolarization and must be indicized to heart rate. It is physiologically prolonged in the first 3 days of life. Values up to 470 and 490 sec are nowadays considered in the range [2, 3], and the dilemma of screening or not infants for the risk of long QT syndrome is not solved at all.

The ECG in the newborn is useful, not-invasive, and reliable. It allows to monitor acute patterns (neonatal tachycardia, post-resuscitation care) as well as to approach relevant symptoms like respiratory distress or cyanosis, and it could be defined as an "oldie but goodie".

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LECT 47

CONGENITAL HEART DEFECT AND GENETIC SYNDROMES

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Congenital heart disease (CHD) is a problem in the structure of the heart that is present at birth, is one of the most common birth defects, affecting up to 8 of every 1,000 babies born. CHD is a significant cause of morbidity and mortality during infancy. The etiology of CHD is complex and heterogeneous, and some factors increase the risk of developing CHD, like prematurity, family history of CHD, genetic syndromes with or without extracardiac abnormalities, maternal conditions (such as diabetes mellitus, hypertension, obesity, thyroid disorders, systemic connective tissue disorders) in addition, drugs taken during pregnancy, and utero infection (eg. rubella).

Genetic factors are important in the etiology of congenital heart defects, and they may be a component of many specific syndromes or chromosomal disorders. The same malformation can be due to different genetic causes, chromosomal anomalies, chromosomal micro rearrangements, and monogenic mutations. The majority of CHD present as an isolated malformation, while 30% have also associated extracardiac malformations (vessels, nervous system, neck, eyes, respiratory organs, oral-facial structures, reproductive and urinary organs, gastrointestinal organs, skeleton, muscles, skin, and other organs).

There are now many of genetic test for the diagnosis of genetic alterations in the child with CHD; these include cytogenetic techniques (Karyotype), FISH, MLPA, array CGH, DNA mutation analysis and next generation sequencing. The cytogenetic techniques identify significant changes in chromosome number or structure and revealed chromosomal aberration in 10% to 15% of neonates with CHD. The more frequent chromosomal abnormalities whit CHD are: trisomy 21 (atrioventricular canal defect), trisomy 18 and trisomy 13 (tetralogy of Fallot, ventricular septal defect, atrial septal defect), monosomy X (coarctation of the aorta, aortic stenosis). Some disorders, including Williams-Beuren (microdeletion 7p 11.23), Di George (microdeletion 22q11.2), have been associated

with a microdeletion that frequently can be detected by FISH technology or MLPA or array CGH. However, in 15-20% of a syndrome with CHD, including RASopathies such as Noonan (PTPN11 12q24.1), Leopard and Costello (HRAS) Kabuki (MLL2, KDM6A) and CHARGE (CHD7), changes occur at the level of a single gene and must be detected by alternative techniques such as next-generation sequencing (e.g., exome sequencing). In a child with CHD, it is essential to determine whether there is an underlying genetic pattern for there may be prognostic information for clinical outcomes. For this reason, the diagnosis of CHD can lead the clinician to suspect a particular syndrome or can suggest specific genetic testing. Moreover, also, the diagnosis of a specific syndrome in a patient can guide to the detection of the CHD, which is more often associated.

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LECT 48

CONGENITAL HEART DISEASE: WHAT PAEDIATRICIANS SHOULD KNOW

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Congenital heart disease (CHD) is present in about 8/1,000 live-born children [1]. Newborns affected by CHD may be cyanotic ("blue") at birth, while others are acyanotic ("pink"). Some CHD are simple and might not require treatment, while others are more complex, thus requiring several surgical interventions to be performed before sorting out. Over the last years, steady technologic progress in the care of these children born with CHD has resulted in their improved management, younger age at completion of surgical treatment, and increased survival rates. This has modified the role of the pediatrician and the training needs for general pediatricians as well. In other words, as children

with CHD are surviving longer, pediatricians are now required to be familiar with the understanding of the long-term complications of CHD. Again, nowadays pediatricians need to know the primary care requirements for these children, recognize those potentially needing further procedures (surgery, interventional cardiac catheterization), bear in mind the latest recommendations for infective endocarditis prophylaxis, respiratory precautions and immunization considerations [2, 3]. Preventing infections starts with good oral and skin hygiene, appropriate nutrition, and common sense. Washing hands frequently, especially during the cold and flu season and avoiding ill contacts is the best way to prevent infections, rather than administering antibiotics. The latter is now indicated only for high-risk patients. Trying to avoid crowded settings is another wise way to prevent infections from happening. CHD children should have routine care and standard immunizations, which are usually recommended for all children. Sometimes further immunizations, such as the influenza vaccine, may be required. If a child has certain CHD, a special monthly immunization for the respiratory syncytial virus may be recommended during the winter months as well. Not only is this true, but also a close monitoring of these children and adolescents in terms of development and behavior is mandatory, as both may be significantly influenced by their condition. This talk highlights the skills needed for pediatricians to identify infants, children, and adolescents with CHD requiring special care with their growth.

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LECT 49

ANESTHESIA AND THE DEVELOPING BRAIN

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Anesthesia-related neurotoxicity in the developing brain has gained an increasing interest in both academic and clinical community for the potential long term harmful effects on neonates and infants undergoing surgery under general anesthesia [1]. This phenomenon has been consistently demonstrated in different animal models such as rats, guinea pigs, piglets, and non-human primates. The administration of inhaled (isoflurane, desflurane, sevoflurane, nitrous oxide) and intravenous (midazolam, ketamine, propofol, opioids) anesthetic drugs have been associated with measurable disruption of different critical processes including neural apoptosis, synaptogenesis, mitochondrial morphogenesis, and autophagy [1]. The prefrontal cortex, amygdala, and hippocampus are exquisitely vulnerable to general anesthesia-induced neuronal death.

Interference with the fine-tuning of cortical developmental processes may not relate to the gross neurologic deficit, but it may cause a variable degree of higher functions disorders, i.e., involving memory, learning, emotions and social interaction [1].

Translation of these non-human animal findings is extremely complex. Current evidence is limited to observational retrospective cohort studies and few clinical trials, whose results are conflicting.

Retrospective cohort studies have reported a higher prevalence of learning disabilities in children that have been repeatedly exposed to general anesthesia before the age of four. Particularly, it was reported an increasing incidence of attention-deficit/hyperactivity disorder, reduced performance on cognitive tests and altered behavior, as heightened emotional reactivity to threats [2]. However, some prospective studies did not detect a significant incidence of cognitive impairment and social or emotional disorders secondary to general anesthesia during the vulnerable period up to four years [1]. The recently published GAS trial provided strong evidence that brief single exposure to general anesthesia, approximately one hour, does not affect cognitive function as evaluated by Wechsler Preschool and Primary Scale of Intelligence at age 5 [3].

Many confounding factors may affect the results of the studies reported by literature, such as the residual burden of disability after surgery, the age of exposure, the total dose of exposure, environmental factors, genetic factors, unknown determinants of vulnerability to anesthesia neurotoxicity, the impact of surgical experience *per se* [1]. However, the US Food and Drugs Administration has added a warning

label to anesthetic drugs addressing neurotoxicity in the developing brain of fetuses, neonates, and infants. This label recognizes the limitations of the available data present in literature, but in consideration of the potential harm, it provides a clinical guideline in choosing which surgery is needed before age three.

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LECT 50

END-OF-LIFE MANAGEMENT: ETHICS VERSUS REALITY

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Recent progress in pediatric and neonatal intensive care have significantly improved the prognosis and chances of survival of critically ill children or extremely premature babies and modified the limits of viability. However, in some situations, when survival is associated with disabilities or an intolerable life for the child and his parents, the application of intensive care may be inappropriate, and treatment limitation with a shift towards palliative care can represent a more humane and reasonable alternative. However, this decision usually involves a three-way relationship among the minor patient, the patient's parents and the physician with a high possibility of disagreements about whether life-sustaining treatment can ethically be withheld or withdrawn taking into consideration socioeconomic status, religious beliefs and dilemma comes down to questions about the value of life with severe physical or cognitive impairments. This presentation will discuss the ethical principles,

the role of parents, and physician's opinion in this decisional process. In the Neonatal and Pediatric Intensive Care Units, disagreements about whether life-sustaining treatment can ethically be withheld or withdrawn are frequent. Usually, the dilemma comes down to questions about the value of life with severe physical or cognitive impairments, and disagreements can go in both directions.

LECT 51

MEDICAL RESPONSIBILITY: THE ITALIAN SITUATION

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Medical liability is a daily nightmare for physicians, including pediatricians, and health professionals have to be considered the secondary victims of this phenomenon. Pediatricians are rarely involved in malpractice suits – as showed by the limited number of lawsuits against them reported by the Italian Society of Paediatrics (SIP) survey [1] – but the economic burden for each compensation is among the highest rewarded by the Italian Courts. To try to solve this problem, the Italian Parliament in 2017 passed a law (Law 24/2017, also known as “Gelli-Bianco”) which proposed new rules to be applied by judges whenever personal damage, allegedly related to medical misconduct, has to be investigated. The pillar of this reform is the fifth article, in which the legislator explains, from a juridical point of view, which has to be the due behavior of a physician. Doctors have to follow the guidelines – the one published in the website of the Superior Institute of Health (ISS) under the National System of Guidelines (SNLG) – and the good clinical practice, only if the former is lacking. Inside this legal framework, the judge should be able to understand – in a personal, easy and direct way – if the physician behavior in the case under scrutiny is correct or if a different approach should have to be employed in order to avoid the damage to his/her patient. We have to agree with one of the underlying assumptions of this reform, namely the one that assesses the duty for every health professional to be able to give – in the actual evidence-based medicine era – sound evidence of the correctness of his/

her choice. However, it is difficult to accept the reduction of a clinical scenario complexity to a few recommendations of a guideline requested by law. Although this choice seemed to the legislator the only, and the right, answer to unravel the long-standing fabric of medical liability, we believe that the aforementioned legal standard may not be considered as the final answer to the medical malpractice crisis. In the 24/2017 law, the civil liability of the physicians working into a State/Regional/Public Health Structure has been led back into the two-piece system (contractual/no-contractual liability) in force before the year 2000. Public or Private Health Structures will be held responsible for the damage suffered by patients under a contract law perspective, while all the health professionals will be considered under a non-contractual liability. This legal decision has to be interpreted as a ‘back to the future’ journey, and it may be explained by the political choice to relieve health professionals from the burdensome commitment to give the judges the evidence of their behavior rightness. If so, hospitals and private health structures will pay the indemnity for the permanent impairment suffered by patients. The structures may have recourse to their employees for the unfair expenditure whenever the health professional behavior is to be considered as characterized by intent or by gross negligence (*culpa lata*).

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LECT 52

MEDICAL RESPONSIBILITY: THE SPANISH SITUATION

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The presentation is focused on the characteristics of medical responsibility in Spain, and on the analysis of the common elements of the cases in a different context, to try to reach references to provide an answer to the increasing of the cases.

What is the reason for the increment in the number of medical responsibility cases? Is it a topic related to medical praxis or it is related to other factors? How

social changes, medical training, use of technology, doctor-patient relationship, social values... are affecting to these demands?

To know the elements involved in these circumstances will help to respond to the situation and to prevent new cases. Moreover, this is not something that we can obtain considering particular contexts; we need to analyze and compare distinct contexts in different countries to reach valid conclusions.

LECT 53

CLINICAL APPROACH TO THE DYSMORPHIC CHILD

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A proper clinical approach is necessary for reaching a definite diagnosis and choosing the best therapeutic and genetic counseling methods for a child with structural abnormalities, by which quality of life can be improved. A definite diagnosis can give clues about the possible course, complications, and prognosis of the disease as well as the best therapeutic and training approaches in a dysmorphic child. Moreover, parents can be counseled and could find an opportunity to participate in family support groups. Clinical geneticist tries to find answers to questions about the structural defect whether; the onset is prenatal or postnatal, the defect is single or with other defects, what could be the underlying mechanism and is it inheritable or not, using the data obtained from the family history, pedigree, physical examination, and diagnostic tests. If a diagnosis cannot be reached despite all, one should try to include the structural defect in one of the categories for which the general approach was predefined.

LECT 54

SLEEP-DISORDERED BREATHING IN A PEDIATRIC SETTING

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INTRODUCTION

Sleep-disordered breathing (SDB) is a general term of wide-ranging breathing problems occurring

during sleep. Obstructive Sleep Apnea Syndrome (OSAS) in children is characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction, which disrupts normal ventilation during sleep and normal sleep patterns. Frequently reported symptoms are sleep apneas and snoring. The causes of respiratory disorders in sleep are multiple and subjective.

METHODS

From the literature, rather than being considered a homogenous disorder, childhood SDB may hence include multiple overlapping phenotypes depending on tonsil and adenoid dimensions, bodily habitus, and craniofacial anatomy.

RESULTS

1. The most common cause of childhood OSAS is enlarged tonsils and adenoids in the upper airway.
2. Obese children display higher prevalence and severity of OSAS. In these children, a high rate of mild sleep respiratory disturbance and ADHD-like symptoms were also reported [1]. In obese children asymptomatic for respiratory sleep problems, SDB might worsen blood pressure through an increase in arterial stiffness [2].
3. Craniofacial disharmony in skeletal diseases is associated with SDB, and the prevalence of this problem in children is worryingly high.

OSAS morbidities primarily involve the neurocognitive, cardiovascular, and metabolic systems. However, there can be significant phenotypic variation in terms of end-organ morbidity for the same OSAS severity. This is likely due to the interplay between genetic and environmental factors.

CONCLUSIONS

Considering the worries of OSAS, such as inattention and behavioral problems, daytime sleepiness, failure to thrive, cardiological and metabolic complications, the benefit of widespread screening and the treatment in children with genetic diseases is undoubtful [3]. The American Academy of Pediatrics (2002) has published guidelines for diagnosis and management of OSAS. Overnight polysomnography remains the gold standard for diagnosing OSAS.

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associated with blood pressure and carotid arterial stiffness in obese children. *J Hypertens.* 2017;35(1):125-31.

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LECT 55

HEART AND PERINATAL PROGRAMMING

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Heart diseases and cancer are the leading causes of death worldwide. Risk charts, capable of predicting the onset of myocardial infarction or stroke in terms of probability, are based on "classic" cardiovascular risk factors (i.e., familial history, smoking habit, diabetes, dyslipidemia, high blood pressure, aging, and gender). However, this traditional approach does not explain why a minority of individuals without the above-mentioned risk factors suffer from cardiovascular accidents. That is the reason why researchers have made their efforts to identify new and previously unmentioned predisposing causes. Among the latter, also preterm birth and intrauterine growth restriction, expressed as low birth weight, have been identified [1]. The complex intrauterine interaction between maternal and fetal environment, which determines birth outcomes and in turn, predicts health and disease over the lifespan is called perinatal programming. When referring to the heart, the adjective "cardiac" is added (perinatal cardiac programming) [2]. Intrauterine growth restriction is one of the most common obstetric conditions, affecting 7-10% of fetuses. Again, prematurity at birth affects around 10% of newborns. Intrauterine exposition to an adverse environment during the highly critical time of development may lead to life-long health consequences, such as markedly increased cardiovascular risk in adulthood. Since their intrauterine life, these fetuses share remodeled hearts with signs of systolic and diastolic dysfunction and displaced apexes. Cardiovascular remodeling also persists into postnatal life, from the neonatal period to adolescence, thus suggesting a primary fetal cardiac programming that might explain the increased cardiovascular risk later in the life of

those who had been born preterm and/or with intrauterine growth retardation [3].

In this review, we summarize the current evidence about fetal cardiovascular programming in fetuses affected by prematurity at birth and growth restriction.

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LECT 56

CYSTIS ECHINOCOCCUS BOTH IN HEART AND LUNG, THE FIRST CASE IN ALBANIA

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BACKGROUND

Echinococcosis is a parasitic disease caused by infection with tiny tapeworms of the genus *Echinococcus*. Cysts of *Echinococcus* can occur in any organ, mostly in the liver (60-70%) and lung (20-30%). Isolated cardiac involvement is rare and occurs in only 0.02-2% of cases. Cyst rupture may cause severe anaphylactic reactions, even death, as a result of the release of cystic fluid.

CASE REPORT

An 11-year-old male was admitted to our hospital due to cough, fewer for the last four days before admission. He did not complain of any other symptoms. His past medical history was unremarkable. The physical examination revealed no specific findings, and there was no sign of respiratory or cardiovascular dysfunction. In chest x-ray, an oval mass was noticed in the right lung with well-defined borders, with regular contours, clear, homogeneous aspect that suggested for Echinococcosis.

The examination was completed with CT lung where it was confirmed the presence of cyst due to *Echinococcus* in the right lung but simultaneously noticed a large heart formation. In echocardiography, a cystic formation was depicted with a clear outline, encapsulated that occupied over the half of the

cavity located mainly in the apex, but that did not prevent the flow in the mitral valve. It was also confirmed the presence of Echinococcus cyst in the left ventricle except the one in the lung.

At first, it was realized heart intervention. The sub-epicardial wall of the cyst was then excised, and its contents were completely aspirated. The cyst was then injected, first with 10 ml of 20% NaCl. The cyst was opened by removing the inner membrane and a part of the outer membrane. Cytology of the aspirated cyst fluid was consistent with the diagnosis of hydatid cyst. After the intervention, the patient suffered from atrial fibrillation. After being treated for several weeks with anticoagulant and antiarrhythmic, atrial fibrillation was converted into sinus rhythm. After about two months, the child underwent another cyst removal in the lung. The patient had an uneventful recovery, and after 16 months, his condition is stable.

CONCLUSION

In cases of an interventricular cardiac hydatid cyst, the combination of surgical resection, and albendazole therapy typically yields excellent results. Surgical excision under cardiopulmonary bypass is the treatment of choice. Chemotherapy in the post-operative period can decrease recurrence in many instances.

LECT 57

YOUNG ADULTS WITH CONGENITAL HEART DISEASE

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Advances in the medical and surgical management of congenital heart disease (CHD) substantially improved survival of infants and children with cardiac defects and, as a consequence, an increasing number of patients, even those with complex defects, reach adolescence and adult life. Recent data suggest that the number of adults with CHD, repaired or unoperated, approaches the number of children with the CHD.

A cure is rarely achieved, and ongoing surveillance and management in conjunction with specialists in this highly specialized field are mandatory in order to provide optimal care for these patients. At present, the level of care for adult congenital heart

disease (ACHD) is not completely satisfactory in many European countries including Italy; patients are often managed as 'special cases' in children's units, or by adult cardiologists with varying degrees of expertise. The resources available for the National Health Systems are more and more reduced with an increasing need for optimization of care.

One of the first steps that should be improved is the Transition program. It is important to distinguish between the different but related concepts of health care transfer and transition. Transfer may be seen as the physical movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems. In contrast, the transition is the purposeful, planned process that addresses the medical, psychosocial, educational, and vocational needs of adolescents and young adults as they move from child-centered to adult-oriented health care systems. In this context, the transition is multidimensional as it involves developmental (adolescent to young adult), situational (discharge and relocation), and health-illness (role changes, self-care of chronic illness) transitions.

Nurses play a crucial role in this process because their care delivery should be addressed to both adolescent patients and their parents. Moreover, nursing care could provide continued contacts between physician, patients, and their families during all their lives.

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LECT 58

METABOLIC EMERGENCIES IN NEONATES

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Even though individually rare, inborn metabolic errors of metabolism (IEM) remain collectively numerous; mainly in a homogenous population with high rates of consanguineous marriages, like most of the Middle Eastern populations.

The presentation of IEM varies depending on the most affected organ, and the nervous system remains the affected organ that leads to most of the complications. A metabolic disease can present with an acute decompensation due to severe acidosis, hyperammonemia, seizures, hypotonia, as well as neurological regression and deterioration. In metabolic disorders, the concept of "emergency" takes up a more extensive definition within the context of every disease.

The diagnosis of IEM remains challenging, accurate knowledge of the major and most frequent IEMs, as well as the appropriate paraclinical workup and management, remains essential in order to correctly treat the acute state as well as to prevent severe exacerbations and complications that might lead eventually to irreversible disability. Early diagnosis and the establishment of the appropriate diet, as well as the accurate orphan drug, can help to keep a healthy, stable child.

The appropriate acute management before the referral to the metabolic specialist plays a major role in avoiding the acute episodes. Having clear guidelines as well as the knowledge of the red flags can help to acquire a better outcome in these patients.

LECT 59

THE BLEEDING NEONATE: OLD DIAGNOSTIC AND OLD THERAPEUTIC APPROACHES IN A NEW ERA

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Haemostasis is a dynamic, age dependent process that begins *in utero* and matures throughout the time from fetal to adult life. The adequate and sufficient haemostatic response of the newborn is closely associated with gestational age, birth weight, vitamin K stores and liver functional maturation. Despite the immature haemostatic system, healthy neonates are able to compensate and do not demonstrate signs of bleeding diathesis or thrombosis. Factors such as infection, asphyxia, trauma etc. are potential triggers, leading to life-threatening haemostatic complications. Thus, early diagnosis and treatment are of great importance. Conventional coagulation tests- such as prothrombin time (PT) and activated Partial Thromboplastin Time (aPTT), which are commonly used in the clinical setting, have limits when it comes to timely diagnosis and treatment of patients. The viscoelastic tests thromboelastography (TEG) and thromboelastometry (TEM) have turned into important tools for early detection of haemostatic complications and guidance for therapeutic interventions at the bedside. Recent studies clearly demonstrate that platelet transfusion at higher platelet count threshold is associated with increased mortality rate in preterm infant, highlighting the need for a restrictive transfusion policy. The use of tests as conducted through TEM/TEG could reduce the need for transfusions. Furthermore, timely intervention with agents like rFVIIa or Prothrombin Complex Concentrates (PCC) could narrow the excess transfusions' detrimental effects.

LECT 60

RETINOPATHY OF PREMATURITY: PAST, PRESENT, AND FUTURE

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Retinopathy of prematurity (ROP) is a developmental vascular proliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. As advances in neonatology have increased the survival of very preterm infants, ROP has become an emerging problem worldwide. The prevalence of ROP varies globally depending on the survival of ELBW babies, recognition of ROP, and

screening programs of the countries. The spectrum of ophthalmological findings in ROP exists from minimal sequelae, which do not affect vision, to bilateral retinal detachment and total blindness. As it is an avoidable cause of childhood blindness, early identification of retinal damage and appropriate treatment can prevent blindness and offer the child better overall development.

Terry first described ROP in 1942 as “retrolental fibroplasia” (RLF) due to the appearance of complete retinal detachment behind the lens. Phelps used retinopathy terminology first in 1981, and in 1984, an international group of pediatric ophthalmologists came together, and name of the disease was changed by consensus of an international group of pediatric ophthalmologists to ROP.

Approximately 60% of childhood blindness is due to ROP in middle-income countries and 10% in developed countries. Studies conducted in developed countries suggest that infants born at ≥ 30 weeks' gestation are not at risk of developing severe ROP. So, guidelines using by these countries including AAP, recommend screening the preterms GA < 30 weeks or $< 1,500$ g and also GA > 30 weeks or 1,500-2,000 g babies with unstable clinical course and cardiopulmonary support. However, these guidelines do not seem to meet developing countries' requirements. Therefore, countries must have their recommendations, and in order to establish a national guideline, they should have their national data. In order to prevent ROP, oxygen delivery in NICU must be optimized (SaO₂ 90-94%), and alarm limits in the NICU must be tight (89% and 95%). Nutrition optimization is essential, and mothers must be promoted and supported for breastfeeding. Reducing blood sampling, especially in the first week of life, is also essential.

LECT 61

EVALUATION AND OUTCOME OF NEUROLOGICAL DAMAGE IN NEWBORNS

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Neurological development is a complex process in which the nervous system reaches its fullness in the adulthood stage. This development begins before birth, continues in both the last months of gestation and in the first months after birth, in response to a continuous remodeling due to the ability

of nerve cells to eliminate excess components through apoptosis. One of the most important and ambitious objectives of developmental neurology is the early identification of those at risk for the development of subsequent disabilities: an early rehabilitation intervention can improve the quality of their life. The most important long-term outcome of periventricular leukomalacia is represented by spastic diplegia, which is also the most frequent motor deficit associated with prematurity. This high incidence seems to be due to the specific localization of the lesion involving the cortico-medullary bundles descending from the motor areas assigned to the movement of the lower limbs. In the presence of larger lesions, which also involve the semi-oval center, tetraparesis can be found accompanied by severe alteration of the intellectual function. The follow-up of the high-risk child and newborn is now established in the most developed countries. Physiotherapy is a relatively recent therapeutic modality in the Intensive Care Units and is performed through different techniques, to reduce respiratory work, maintaining airway viability and improving ventilation and gas exchange, improving neurosensory skills. A sensitive period for performing an intervention with a set schedule is from birth to 24 months of the correct age. The program is tailored to the child and his family. An intervention program must promote the neurobehavioral development of the child, the quality of the organization and the relational, sensorial, motor and cognitive skills and their integration, with the aim of an adequate development, without the pretension of modifying or accelerating its natural learning.

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LECT 62

THE INFANT OF DIABETIC MOTHER

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The term diabetes mellitus identifies a group of metabolic diseases characterized by hyperglycemia associated with disorders of secretion or insulin sensitivity or both. Type 1 diabetes (TD1) that represents the 3-6% of the total cases of diabetes is classified among the so-called autoimmune diseases, and generally, it occurs during infancy or adolescence with a peak of incidence between age 10 and 14. Sardinia, together with Finland, is the region that presents the highest number of new TD1 cases per year, reaching an incident of over 50 cases per 100,000 inhabitants. Type 2 diabetes (TD2) is the most common form of diabetes (about 90% of cases), and it generally manifests after 30-40 years of age. Lastly, every case in which there is a high level of circulating glucose for the first time during pregnancy is defined as gestational diabetes (GDM). This condition occurs in 4% of pregnancies.

Due to the short- and long-term complications of diabetes (among them: cardiovascular diseases, neuropathy and diabetic nephropathy), the healthcare, social and economic impact has imposed on a worldwide level the search for organizational pathways that minimize as much as possible the incidence of the acute events or the debilitating complications that imply extremely high costs both direct and indirect. In Italy, nowadays, the consumption of the healthcare resources of diabetic people is 2.5 times higher than that of non-diabetic people of the same sex and age. TD1, together with GDM, is one of the diseases that worsen the course of pregnancy, increasing the risk of maternal-fetal complications on the short and long term. Referring to neonatal health, diabetes in pregnancy, related to a higher risk of congenital malformations, mortality, and morbidity represents the most frequent cause of

embryo-fetopathy. The incidence of malformations in neonates of diabetic mothers is estimated to be from 2 to 4 times higher than that found in the general population, and the most affected organs are heart, central nervous system, kidney, and the skeleton. In particular, the incidence of congenital cardiopathy is about 5 times higher when compared to the general population. Moreover, even in neonates of diabetic mothers without congenital cardiac malformations, sonographic studies showed hypertrophy of the intraventricular septum and the ventricular walls. Nevertheless, according to the data in the literature, it is not possible to evaluate the incidence and the specific risk of cardiomyopathy in patients with hypertrophy of the septum at birth.

Several studies on animal models highlighted that the exposition to a hyperglycemic and hypoglycemic environment in the uterus could lead to a reduced glucose tolerance at birth that persists in adulthood, regardless of genetic predisposition of the subjects. Although metabolic alterations such as hyperinsulinemia and hypoglycemia had been observed, metabolic pictures that can be considered “specific” of this pathology had never been described in neonates of diabetic mothers.

Several studies in literature affirm that environmental factors that affect the fetus can influence its prenatal development determining structural and functional alterations that could be irreversible and persist in the post-natal life increasing the risk of developing metabolic diseases in adulthood such as obesity, TD2, and metabolic syndrome. In this scenario, it seems clear that the development of analytical strategies more and more sensitive and useful for the early diagnosis in subjects at risk of developing diabetes can provide important contributions to reduce the enormous clinical, social and economic costs of this pathology. The new “omics” sciences such as metabolomics and microbiomics seem to be able to characterize the metabolic phenotype of neonates of diabetic mothers and detect a “biochemical fingerprint” useful for the recognition of potential biomarkers related to diabetes. The ultimate goal of these sciences is to design a nutritional and therapeutic program different for each patient.

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LECT 63**MENTAL HEALTH IN CHILDREN WITH NEOPLASMS**

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Mental health in children with neoplastic pathology seems a problem that has not been done as much as it should be. Further studies and research are needed. By curing the underlying pathology, we sometimes forget that close or distant mental health problems, related to pathology itself, hospitalization, therapeutic interventions, etc., may often emerge in the first plan, because of their prognostic importance and their severe consequences. The aim of diagnosing and treating as early as possible mental health problems in children with cancer has a direct positive influence on minimizing or eliminating the near or far-reaching harm both in the health and social aspect of the patient. Naturally, the best effect would be achieved when preventing this problematic, and this would be related to a complete knowledge of this problematic, both from the family, the environment where the child lives and learns and from all staff involved in the treatment of the child. Good knowledge would also influence the realization of contemporary prevention and treatment schemes for multidisciplinary management of these problems, in line with contemporary European standards. In my presentation, I tried to give an updated summary of the diagnostic, therapeutic and preventive attitudes, contemporary, for these problems as well as examples from the modest experience in our service.

MATERIALS AND METHODS

The most recent literature sources (2000-2017) were used to select theoretical information about mental health disorders in pediatric neoplasm and to analyze the most reliable contemporary experiences regarding accurate diagnosis and especially appropriate therapeutic intervention of these changes. We also relied on reports from the WHO or the structures and institutions of the strategy to develop some basic recommendations regarding integrated management of mental health changes in pediatric oncology. For the analysis of our experience, we relied solely on the presentation of our few cases, followed during their hospital

stay. Hospitalization cards, day hospital charts, informational talks with doctors, psychologist, chief nurse, social worker were used for this.

CONCLUSIONS

Mental health in children with neoplastic pathology requires a multidisciplinary approach. In young patients, the new hospital environment creates a sense of fear, loneliness, abandonment by family, society, and all activities of daily life that until recently were a source of pleasure and joy. Painful techniques, chemotherapeutic preparations that affect the peripheral and central nervous system, also have a negative impact. The most common changes are: mood disorders, anxiety disorders, depressive states, obsessive-compulsive disorder, etc. In this situation, the help of an infantile neuro-psychiatrist prescribing the most appropriate therapy, in close cooperation with a physician, parent, psychologist, etc. is necessary

LECT 64**GYNECOLOGICAL PROBLEMS IN CHILDREN AND ADOLESCENTS**

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This paper describes the most frequent gynecological problems which affect the girls during childhood or the early gynecological life.

Vulvovaginal complaints account for 80-90% of outpatient pediatric gynecologic visits. Most cases may be attributed to vulvovaginitis, but other less common conditions should be taken into account. The prepubertal child is particularly susceptible to vulvovaginitis. Although vulvovaginitis in prepubertal girl may be often attributed to poor hygiene or non-specific irritant, clinicians should be able to recognize specific vulvovaginitis, due to infective agents, and other vulvovaginal conditions, such as vulvar diseases or vulvar manifestations of systemic disease, whose symptoms may overlap.

Since the nineties, why, when, and how a "first gynecologic exam" should be performed in teens have been debated by gynecologists and pediatricians in Italy and abroad. With several statements, the latest of which in 2014, the American College of Obstetricians and Gynecologists – ACOG recommends a

"first gynecologic visit to all 13-15 years aged adolescents, with preventive and educational purposes". This evaluation should be performed according to the developmental level of each girl in an adolescent-friendly and confidential environment. Besides detailed counseling about pubertal development, menstruation, contraception, STDs and sexual abuse prevention must be performed.

Affecting up to 85% women, dysmenorrhea is the most frequent genital complaint in teenage and the leading cause of school absenteeism, with severe social relapses. Primary dysmenorrhea, namely without underlying pelvic pathologies, occurs in 90% cases; in the remaining 10% cases, it is later. Secondary dysmenorrhea is associated with well-defined pelvic pathologies, mainly endometriosis, and obstructive genital anomalies.

Dysfunctional Uterine Bleeding (DUB) represents a particular type of Abnormal Uterine Bleeding (AUB); AUB is an atypical loss of blood from the uterine cavity that occurs outside of the menstrual cycle. It is often a source of much anxiety for adolescents as well as their parents and is defined in the United States as an excessive, prolonged and irregular bleeding of the endometrium (frequency < 21 days; duration > 7 days; daily use of sanitary towels/tampons > 1/1-2 hours), that does not cause pain and do not have any organic cause, so much so that it is frequently considered to be a symptom of anovulatory bleeding. Others frequent pathologies can affect the ovarian activity, causing menstrual disorders as oligomenorrhea or secondary amenorrhea, in particular, eating disorders or polycystic ovarian syndrome.

In order to prevent and eventually treat these frequent problems, the Italian Society of Paediatric and Adolescent Gynaecology – SIGIA proposes a peri-menarchal gynecologic evaluation as an integration of paediatric routine health assessments, to be performed in all 11-15 years aged girls, with different operating methods in sexually active or non-sexually active girls and in symptomatic or asymptomatic ones.

LECT 65

THE SCHOOL OF PEDIATRICS IN EMERGING COUNTRIES: THE ROLE OF ITALIAN INTERNATIONAL COOPERATION

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In July 2018 the world was hosting 7,503,828,180 inhabitants, 25.29% of which children (0-14 years). The global growth rate is 1.05%, equivalent to 2.5 every second (4.3 every second last year), 78,314,400 neonates in a year. More than 2.5 mln of these neonates will die before one year of age, in the overwhelming majority in Africa. By the end of XXI century, China inhabitants will decrease to slightly more than 1 bln, Europe will have 90% of the actual population, Americas almost stable, from 2060 on also India will decrease, while Africa will more than triple reaching some 4 bln. The burden of infant mortality will be borne almost totally by Africa, with unbearable variations among countries (Somalia and South Sudan > 90%, Slovenia 1.6%). Among the causes is the lack of MD (estimated at 4 mln worldwide = 1 mln pediatricians), dramatically lower in Africa (Sierra Leone 1 MD /33,000 inhabitants, Italy 1/244). There is 1 pediatrician every 1 mln inhabitants in Malawi, 1.3 in Sierra Leone, 1.7 in Sudan, 2.5 in Tanzania. Pediatric societies affiliated to International Pediatric Association (IPA) are 35 out of 54 countries in Africa.

Developing curricula for postgraduate medical training is a challenge in the 168 African Medical Faculties (African Medical Schools Association). Pediatrics, together with Medicine, Surgery, and Ob&Gyn is the most popular specialization to be taught, but available posts are still too scanty. Since 2008, the intra-continental project African Paediatric Fellowship Programme (APFP) based in University of Cape Town, South Africa, the biggest children's hospital in sub Saharan Africa, graduated 73 specialists in all pediatric subspecialties in 7 years, investing 22,500 \$/year for 2 to 4 years, a great achievement also to avoid the brain drain of young doctors specializing abroad and not to come back their homeland.

The role of Italian Universities in helping to improve this training in the general framework of international academic cooperation can be twofold: a) helping African universities to improve their curricula via mutual consultations on structural issues, missions of visiting professors or, more recently, teleconferencing; b) exchanging trainees to improve their training in a unusual setting or offering short-term intensive courses to maximize results and avoid brain drain.

The University of Pavia is implementing medical cooperation projects in Mogadishu (revitalizing the

Medical Faculty at Somali National University), in the pediatrics departments of Ziguinchor in Senegal, Malindi in Kenya, Chirundu in Zambia, Balaka in Malawi. Out of Africa, Pavia is the University coordinating an Erasmus+ CBHE project aimed to update curricula in Pediatrics, Pediatric Surgery and Pediatric Neurology in 8 Universities in Kazakhstan, Uzbekistan, and Tajikistan, with the partnership of Ulm and Krakow Universities. Synergy, Strategy, and Sustainability are the keywords that should inspire all cooperation activities in emerging countries, not only in academic projects.

LECT 66

CARDIOSURGERY IN EMERGING COUNTRIES

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Congenital heart diseases (CHD) are present in nearly 1% of live births; according to WHO, there are 1.5 million newborns affected by CHD per year and more than 4 million children waiting for cardiac surgery treatment worldwide. The majority of these children (~90%) could be treated, saved and subsequently have a good quality of life but unfortunately, in developing countries with suboptimal care or no access to care, they are destined to die.

There are various well-known organizational models to start a cooperation project in pediatric cardiac surgery in a developing country. One possible model is to create a long-term collaboration with a stable local partner, to have a big financial investment and a long period of development (10 years or more). It is probably the most difficult model, but it is the only one with the greatest guarantee of success in terms of sustainability and autonomy.

LECT 67

PEDIATRIC FELLOWS IN AFRICA

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Africa has a significant burden of childhood disease, with relative few skilled health care professionals.

The World Health Organization (WHO) estimates that children in low- or middle-income countries are 16 times more likely to die before 5 years of age compared with children in high-income countries. CUAMM is the largest Italian Non-Governmental Organization (NGO) for the promotion and protection of health in Africa operating in 8 countries, including Angola. The NGO implements development projects to foster maternal and child health by strengthening the local public health system. The Junior Project Officer Program (JPO) was developed by CUAMM in order to recruit residents in Pediatrics, interested in Tropical Pediatrics and International Cooperation. The Pediatric Fellow was established by the Department of Pediatrics and Child Health, Hospital da Missão Católica do Chiulo, a rural hospital in one of the poorest regions of Angola, Cunene Province, where Angolan and Italian doctors cooperate to promote maternal and children health. This Department serves as a Referral Centre and can take care of children suffering from a spectrum of complex diseases, specific to Africa. Residents spend 6 months abroad and, during this period, they will be orientated, tutored, and guided in various aspects of Pediatric Clinical Practice by another CUAMM Specialist who also serves there. The program aims at enhancing clinical practice and pediatrics teaching, by increasing expertise in clinical practice and familiarity with protocols appropriate to the continent's burden of childhood disease. The knowledge and skills acquired by fellow students will empower future pediatricians to conduct optimal pediatric clinical practice either in a general pediatric unit or in a pediatric unit of a developing country.

LECT 68

AUTISM: PATHOGENESIS, PREVALENCE, AND COMORBIDITY

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The prevalence of Autism Spectrum Disorder (ASD) has increased substantially during the last decades. From the 1960s and onwards the reported prevalence of ASD has increased more than 30-fold which has spurred considerable public debate. This talk will investigate whether this increase is real or an administrative effect. In this presentation

results from the Child and Adolescent Twin Study in Sweden, a nation-wide Swedish twin study comprising more than 30,000 individuals will be presented. Parent-reported data from the Autism, Tics, ADHD and other Comorbidities inventory will be contrasted to register-based clinical diagnoses in order to compare diagnostic trends and to resolve whether the increasing prevalence is associated with a change in the ASD pathogenesis.

Furthermore, the highly heterogeneous ASD phenotype will be illustrated in a genetically sensitive design. The annual prevalence of the autism symptom phenotype was stable during the 10 years, while registered diagnosis monotonically increased. There is an average decrease of 50% in autism symptomatology in those diagnosed with ASD at ages 7-12. Irrespective of prevalence changes the pathogenesis behind ASD appears to be constant. Half of the individuals with ASDs had four or more coexisting disorders and only 4% of individuals with an ASD did not have any concomitant disorder. Taken together, administrative changes, affecting the registered prevalence, rather than secular factors affecting the pathogenesis accounts for the lion's share of the increase in individuals diagnosed with ASD. Finally, ASD seldomly occurs alone, rather coexistence of other disorders is the rule rather than the exception.

LECT 69

OMICS IN AUTISM

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Autism is a major psychiatric disorder characterized by some abnormalities, including repetitive behaviors, failure in speech, and non-oral communication, a deficit in social responsiveness with restricted interests. Additional traits include sensory modulatory dysfunction, varying levels of cognition and motor disturbances, and poor eye contact. Recently, the term autism has been replaced by an umbrella term, autism spectrum disorder (ASD), embracing a wide range of behavioral, communication, and social disorders, Asperger's syndrome, and other related conditions. Moreover, children with ASD have an excess of minor physical anomalies, which are defined as morphological deviations present in less than 5% of the population.

Unfortunately, no one knows for sure and definitively what causes autism. The prevalence of ASD has shown an extraordinary increase over time worldwide, documented both by data from the World Health Organization (WHO) and data obtained from systematic reviews and public surveys. WHO estimated 0.76% of the world's children with ASD in 2010; similar data (0.70%) were reported in 2017 by Lyall K et al., even though epidemiological estimates can considerably vary by demographic factors, namely ethnicity and socioeconomic status, as well as diagnostic criteria. In the United States, a very recent survey performed in 11 states on children aged 8 years assessed an overall prevalence of 16.8 autistic children every 1,000 non-ASD children (equal to 1 child every 59), with a higher prevalence in boys (26.6 per 1,000) than in girls (6.6 per 1,000). Worldwide, autism affects 2 to 3 times more males than females. ASD develops from the interplay between a multitude of factors: genetics, epigenetics, environment, socioeconomic status, maternal and neonatal infections, prenatal nutrients (i.e. folic acid), immune system, gut microbiota composition, maternal exposure to potentially toxic drugs (e.g. thalidomide), environmental toxicants, and infant feeding (breastfeeding or formula feeding). ASD develops from the interplay between a multitude of factors: genetics, epigenetics, environment, socioeconomic status, maternal and neonatal infections, prenatal nutrients (i.e. folic acid), immune system, gut microbiota composition, maternal exposure to potentially toxic drugs (e.g. thalidomide), environmental toxicants, and infant feeding (breastfeeding or formula feeding). Genetic etiology ranges from identifiable monogenic syndromes to large chromosome imbalances. Chromosomal microarray analysis (CMA) is recommended as the first-tier genetic test for individuals with ASD with a yield ranging from 7.0% to 9.0%. Whole exome sequencing (WES) on research cohorts of individuals with ASD have highlighted sequence level *de novo* mutations in the etiology of ASD. Therefore, the role of genetics cannot be dissociated from the context of epigenetic mechanisms and specific interactions. Despite a worldwide agreement on the urgent need for timely identification of ASD as early in life as possible, most children with ASD are diagnosed far too late. The delay in diagnosis hampers initiating effective measures for managing cognitive impairment and adopting educational training both for parents and preschool staff. Despite this wholly unsatisfactory scenario, encouraging perspectives are emerging

from new insights into non-genetic factors involved in the origin of ASD and from advanced diagnostic tools, namely metabolomics.

Metabolomics is the study of the small molecules, namely metabolites, contained in body fluids as well as in human cells, tissues or organs. Metabolites are involved in primary and intermediary metabolism. The Metabolomics Society defined metabolomics as "the study of metabolic changes". The term "metabolomics" is equivalent to metabolite target analysis, metabolite profiling, metabolic fingerprinting, metabolic profiling. Metabolomics provides a functional readout of changes determined by genetic blueprint regulation, protein abundance and modification, and environmental influence. Analysis of published data from the literature shows that the initial metabolic perturbations recognized in autistic subjects consist of: high concentrations of mammalian-microbial cometabolites; nicotinic-acid metabolism; production of cellular energy due to mitochondrial dysfunction; antioxidant status; amino acid metabolism. One of the most relevant factors modulating gene expression by epigenetic mechanisms is fetal/neonatal gut colonization and dysbiosis. There is a broad worldwide consensus on the role of intact gut microbiota in shaping brain neurochemistry and emotional behavior. Gastrointestinal flora can be considerably altered by several environmental factors, such as maternal bacterial flora and diet; perinatal antimicrobial use; mode of birth (spontaneous delivery or caesarian section); type of feeding; dietary intake. Notably, psychological stress during pregnancy and at birth can induce changes in the composition of gastrointestinal microbial flora. Gut dysbiosis raises abnormal metabolites and their escape into the bloodstream; most of them are neurotropic. This means that they rapidly pass the blood-brain barrier and then could act as neurotransmitters or could modify biochemical pathways within the central nervous system, altering neurotransmitters synthesis and release. In conclusion, alterations in the composition and metabolic products of the gut microbiome have been implicated in the complex pathophysiology of ASD and these alterations can be quickly revealed by changes in urine metabolome of newborns. The early identification of risk factors for ASD can improve children outcome by early therapeutic interventions such as gut microbiota transplantation. This implies a drastic reduction in the severity of ASD symptoms and, in turn, a better socio-relational outcome and a considerable saving of money.

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LECT 70

PANDAS SYNDROME: WHAT IS NEW?

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The Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is characterized by an abrupt onset of obsessive-compulsive disorder (OCD) or severely restricted food intake. This condition is accompanied by severe associated neuropsychiatric symptoms: separation anxiety; irritability, aggression and/or severely oppositional behaviors; emotional lability and/or depression; sensory or motor abnormalities with choreiform finger movements; academic decline related to attention and memory deficit. Sleep disorders have been clinically described in about 80% of patients with PANS. The diagnosis of PANS is made by "exclusion", as the individual PANS symptoms overlap with a multiplicity

of psychiatric disorders, such as schizophrenia, depression, ADHD (Attention Deficit Hyperactivity Disorder), Tourette's syndrome and bipolar disorder. However, the abrupt and simultaneous onset of these symptoms makes it possible to differentiate the PANS from other psychiatric conditions. PANS is characterized by a large number of related disorders with multiple etiology, ranging from autoimmune or autoinflammatory diseases, immunodeficiency syndromes and recurrent infections. In particular, different investigators observed that the abrupt and simultaneous onset of OCD disorders were preceded by a bacterial or viral infection, such as varicella, influenza, and infections from *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, *Group A Streptococcus*, Epstein Barr and *Borrelia burgdorferi*. It has been highlighted how infections can trigger autoimmune responses that cause or exacerbate OCD or tic disorders (including Tourette's syndrome) through a process analogous to Sydenham's chorea. Over time, several researchers accumulated more evidence to support the hypothesis that PANS were closely associated with a variety of infections, including *Mycoplasma pneumoniae*. Alternatively, in the absence of established infection, these conditions could be triggered by environmental factors and/or metabolic disorders. The diagnosis of PANS is still under debate and not well defined. The supposed autoimmune pathophysiology of PANS can depend not only from the presence of neuronal antibodies but also from the action of neuroactive cytokines, IL-17A, IFN- γ , as inflammatory mediators, So, it is essential to better understand the pathogenetic mechanisms of PANS and to identify disease-specific biomarkers. In recent years, different metabolomics studies have been conducted in order to better characterize biochemical and biological mechanisms underlying neurological disorders in the pediatric population. The study of the metabolome in the field of PANS, a condition still characterized by many doubts, could be essential to define its pathogenesis and characterize possible biomarkers.

LECT 71

SUBSTANCE USE AND MISUSE IN ADOLESCENTS

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Substance use, including alcohol, tobacco, and other illicit drugs is an important cause of morbidity and mortality in adolescents globally. Not only addiction or abuse of substances but also the use and misuse of substances in adolescence are associated with major physical and mental health problems. Clinically, the use of substances generally proceeds as a continuum process across stages in adolescents which begins with experimentation, then learning the mood swings, continues with preoccupation with these mood swings and finally leading to problem use and dependence. Although some adolescents may skip stages, the primary focus for clinicians working with adolescents would be encouraging and normalizing abstinence and refusal skills. In this presentation, we will discuss why adolescents use substances developmentally including high-risk behaviors, conflict with the authority, the effect of peers, not being able to refuse, issues with identity development, testing the boundaries, body image distortion and physical, sexual or emotional abuse. Self-medication would be another cause of substance use in adolescents which should be differentiated from the other developmental issues since it would not be possible to help these teens without proper treatment of the underlying causes such as depression, anxiety or attention deficit hyperactivity disorder. We will also discuss how to obtain a thorough history of substance use and interview the adolescent. Motivational non-judgmental interview and reconciling confidential health care with parental involvement should be considered with individually determined limits of confidentiality in adolescents with substance use and misuse. Also, rehabilitation of substance abuse and addiction will be discussed with the harm reduction versus abstinence approaches in youth.

LECT 72

CHILDHOOD AND ADOLESCENCE PSYCHOPATHOLOGY? THE CAPICE PROJECT

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Longitudinal studies show that about 50% of children and adolescents with psychopathology

continue to have mental disorders in adulthood. The developmental trajectory of childhood and adolescent psychopathology can have a homotypic (when a particular psychiatric disorder predicts itself at a later time point) or heterotypic (when a particular disorder predicts another disorder at a later time point) continuity. Recent data show that heterotypic continuity is common and is not an artifact of uncontrolled homotypic continuity. In this context, a relevant clinical question concerns how to increase the accuracy and precision of predictive models to delineate the trajectory to mental disorders in adulthood. One possibility is to integrate accurate clinical information with data coming from omics approaches, such as genomics, transcriptomics, and epigenomics. One attempt in this direction is currently being made by the Marie-Curie training network CAPICE (Childhood and Adolescence Psychopathology: unraveling the complex etiology by a broad Interdisciplinary Collaboration in Europe). This European Union (EU) funded network brings together 8 population-based birth and childhood (twin) cohorts to investigate the causes of individual differences in childhood and adolescence psychopathology, in close collaboration with the EARly Genetics and Life-course Epidemiology (EAGLE) consortium. The cohorts have unique longitudinal information on lifestyle, family environment, health, and emotional and behavioral problems as well as (epi)genome-wide genotypic data, sometimes even for the parents. The focus of CAPICE is mainly on clarifying the etiology of common psychiatric symptoms in childhood and adolescence, which might include depression, anxiety, but also an alteration in cognition, particularly attention deficits, or behavioral and personality disturbances. Besides the identification of (epi)genetic variants associated with these phenotypes, CAPICE is poised to shed light on their interplay with the environment in influencing the persistence of psychopathological symptoms. Here, we briefly review the main aims focusing on preliminary results of the consortium with a specific focus on genomic findings obtained in the context of CAPICE.

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LECT 73

ANOREXIA

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In newspapers and magazines, on television, on the street and in the park, there are discussions about weight loss and silhouette. While adults can ignore these messages, the children understand that being slim is the highest quality. A lot of the guilt belongs to the press because it promotes the very slim celebrities and the idea that success and beauty are dependent on the small number of calories. Everyone is focused so much on the silhouette that they managed to transform the normal relationship with food into an artificial one with priority in calorie counting. It would be essential for parents to get used to their children from younger ages with healthy eating habits: regular meals and a balanced diet. Anorexia nervosa is an eating disorder observed with increasing frequency, especially among adolescent females. No consensus exists concerning the causes of the disorder. Social, psychosexual, family emotional climate, biological theories, and a regression hypothesis have been advanced to explain the phenomenon. The major characteristics of the disease are 25% loss of body weight, use of various means to lose weight, weight phobia, preoccupation with food, body image disturbances, as well as numerous associated medical conditions: bradycardia, hypotension, dehydration, hypothermia, electrolyte abnormalities, amenorrhea, metabolic changes, and abdominal distress.

LECT 74

NEONATAL TRANSPORT IN MIDDLE EASTERN AND MEDITERRANEAN COUNTRIES: PROCESSES, STRATEGIES, AND CHALLENGES

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INTRODUCTION

The development of Neonatal Transport Service (NTS) started about 50 years ago, together with the establishment of the first Neonatal Intensive Care Units (NICUs). Currently, NTS has become a real mobile Intensive Care Unit able to provide the best care when the mother's transfer is not possible. It is worldwide known that today, NTS is considered one of the milestones reached by the regionalization of

perinatal care. Differences in equipment, education, and clinical competencies are responsible for variable outcomes from region to region. Therefore, it is important to avoid a lack of standardization in these factors.

NTS ISSUES AND STRATEGIES

Many regions of the Middle Eastern and Mediterranean countries have NTS with the same key elements: team, equipment, ambulance/aircraft/helicopter service, training, administrative and supporting staff, clinical competencies, insurance coverage, audit, and feedback. The above key elements belong to the clinical governance and are today the most important because clinical governance has to be applied to NTS as well. Newborns belong to a particular patient population with different needs than adults. Having a dedicated transport team improves outcome and neonatal survivals. About the training, the key elements for an efficient team are leadership, flexibility, independence, critical thinking, favorable judgment, problem-solving skills, interpersonal and communication skills; these elements are reinforced by simulation, and appropriate Crisis Resource Management is a standard widely accepted. In our era of limited financial resources for health-care systems, NTS sustainability starts to become a problem, and alternative models have to be considered. Transport teams need all the equipment necessary to ensure proper care and to guarantee safe ground, water, and air transport. Policies and procedures are necessary to guide transport teams, and communication with families is fundamental.

CONCLUSIONS

Taking into account both financial issues and advances in provided technologies, NTS remains pivotal to neonatal care improvement, NICU beds, financial, human, and technical resources optimization, appropriateness of care, risk management, and neonatal networks enhancements, and last but not least newborn protocols sharing and reinforcement.

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LECT 75

ULTRASOUNDS IN NEONATOLOGY

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Central venous access is an important measure used in neonates whether being a perioperative measure for children undergoing cardiac procedures for congenital heart diseases or as a mean of nutrition in neonatal enteral malnutrition and drug administration in pediatric. Central catheters can be divided into two categories: a) peripherally inserted central catheter (PICC) line or b) centrally inserted central catheters. Although these two modalities practically have the same aim, knowing the differences between them is imperative for the correct choice of the procedure for ameliorating patient outcomes. Many studies have been previously performed that report the indications for central venous access with practically no absolute contraindications. These indications include central venous pressure (CVP) monitoring, poor venous access, volume resuscitation, and prolonged venous access in critically ill patients, total parenteral nutrition (TPN), cardio-pulmonary resuscitation and drug administration. Centrally inserted catheters have evolved from being blindly inserted catheters, to being placed under direct visualization using ultrasound guidance. Since its first use back in the '90s, ultrasound-guided insertion of central venous catheters has gained attention, and successful attempts have been made to improve this technique. US-guidance initially used acoustic Doppler techniques but is now mostly replaced by two-dimensional (2D) imaging and internal jugular vein (IJV) being the preferred site of insertion by the US over the femoral and subclavian vein.

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LECT 76

THE ROLE OF VITAMIN D IN NEONATOLOGY AND PEDIATRICS

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Vitamin D (VD) is a group of fat-soluble secosteroids, including vitamin D₃ and vitamin D₂. In nature, there are very few dietary sources of VD, and its content is small in the usual diet of children. Moreover, human milk and infant formulas are low in VD. Sun exposure is the main source of VD: in fact, UV-B radiation converts 7-dehydrocholesterol in previtamin D₃, which isomerizes to VD₃. Then, VD₃ is activated through sequential hydroxylation steps in the liver and kidney. VD is essential to ensure normal growth and development. Its action is involved in the mineralization of the developing bone tissue and the endochondral ossification of the growth plate. Recent studies have shown that VD also has complex immunoregulatory properties and other important extra-skeletal effects.

VD deficiency in pregnancy has been associated with adverse maternal, fetal, and neonatal outcomes. Globally, VD deficiency (25(OH)D < 20 ng/ml) is found in 54% of pregnant women and 75% of neonates, and severe VD deficiency (25(OH)D < 10 ng/ml) in 18% of pregnant women and 29% of neonates. Maternal VD insufficiency has been associated with preterm birth, with an inverse dose-response relation. Moreover, prenatal VD deficiency exposes to an increased risk of acute respiratory infections during the first 3 years of life. VD supplementation in pregnancy would be able to reduce the risk of preterm birth, pre-eclampsia, and maternal bacterial infection, but it would not increase offspring whole-body bone mineral content. A recent Italian Consensus recommends VD supplementation (600 IU/day) in all pregnant and breastfeeding women from the beginning of pregnancy. Higher dosages (1,000-2,000 IU/day) should be given to women at risk for VD deficiency. Routine screening during pregnancy is recommended by some authors, whereas others suggest considering VD testing in the presence of multiple risk factors for VD deficiency.

In Europe, the prevalence of VD deficiency varies from 4-7%, 1-8%, and 12-40% in 1-6 years, 7-14 years, and 15-18 years age groups, respectively. The prevalence of rickets varies among countries and ethnic groups between 2.9-95/100,000. Indoor

sedentary lifestyle habits, resulting in insufficient sunlight exposure, current "epidemics" of obesity, and other preventable risk factors may contribute to the re-emerging hypovitaminosis D in children and adolescents living in developed countries. In the pediatric population, VD status has been classified as sufficiency (> 30 ng/ml), insufficiency (20-29 ng/ml), deficiency (< 20 ng/ml), and the severe deficiency (< 10 ng/ml). Currently, screening of VD levels is recommended only for children with risk factors such as dark skin, chronic therapy with systemic glucocorticoids or anticonvulsants, malabsorption, frequent fractures, and low bone mineral density. VD supplementation is recommended in all infants in the first year of life. Subsequently, it should be individualized based on the presence of risk factors for VD deficiency.

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LECT 77

CRISPONI SYNDROME

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INTRODUCTION

Crispioni/cold-induced sweating syndrome type 1 (CS/CISS1) is a rare autosomal recessive disorder characterized by a complex phenotype with high neonatal lethality, associated with hyperthermia and feeding difficulties in the neonatal period, scoliosis and paradoxical sweating induced by cold since early childhood. Less than 100 cases have been reported in the literature, and most of them originate from Europe, especially from the Mediterranean region with Italy and in particular Sardinia and Turkey the most affected countries. CS/CISS1 is

caused by biallelic variants in the CRLF1 gene and belongs to the family of “CNTFR-related disorders” with overlapping clinical features including cold-induced sweating syndrome type 2 (CISS2) and Stüve-Wiedemann Syndrome (STWS), caused by biallelic variants respectively in the CLCF1 and the LIFR genes. CISS1 and CISS2 are clinically indistinguishable, and the term CS/CISS covers both disorders until a molecular diagnosis is made. The CRLF1 and CLCF1 proteins form a secreted complex, which acts on cells expressing the ciliary neurotrophic factor receptor (CNTFR). The binding of the CFRL1:CLCF1 complex to the CNTFR triggers the downstream signaling primarily involved in the development and maintenance of the nervous system.

MATERIALS AND METHODS

The combination of typical CS/CISS symptoms and disease-associated variants in CRLF1 or CLCF1 are the prerequisites for establishing the diagnosis. A subset of CS/CISS cases remains yet genetically unexplained after CRLF1/CLCF1 sequencing. The differential diagnosis in CS/CISS has rapidly changed with the use of whole-exome sequencing (WES), and variants in other genes have been recently found associated with a CS/CISS-like phenotype.

RESULTS

These genes include KLHL7, NALCN, MAGEL2, and SCN2A, already involved in the pathogenesis of former known disorders with a dominant/*de novo* hereditary pattern. So, WES disclosed unpredicted differential diagnoses in people with a CS/CISS-like phenotype, including congenital contractures of the limbs and face, hypotonia, and developmental delay (CLIFAHDD), Schaaf-Yang (SHFYNG), and early infantile epileptic encephalopathy-11 (EIEE11) syndromes.

CONCLUSIONS

These results strengthen the importance of molecular diagnostic confirmation. Considering the significant phenotypic similarity between CS/CISS and other disorders, especially in the neonatal period, correct counseling should be carried out only when the clinical suspect has been proved by molecular genetic analysis. An accelerated and precise diagnosis can ameliorate patient care, and it is critical to achieving a specific clinical follow-up, which is long-standing and requires a multidisciplinary approach. Presently, no therapy is available for CS/CISS, except for the paradoxical sweating induced by cold, which can be successfully treated with clonidine/amitriptyline or moxonidine.

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LECT 78

TYPE I DIABETES: THE ROLE OF THE EXPOSOME

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Type 1 diabetes (T1D) results from autoimmune destruction of insulin-producing beta cells that requires lifelong insulin treatment. While significant advances have been achieved in treatment, prevention of complications, and quality of life in diabetic people, the identification of environmental triggers of the disease is far more complex. The island of Sardinia has the second-highest incidence of T1D in the world (45/100,000), right after Finland (64.2/100,000). The genetic background, as well as the environment of the island's inhabitants, makes it an ideal region for investigating environmental, immunological, and genetic factors related to the etiopathogenesis of T1D. Several epidemiological studies, conducted over the years, have shown that exposures to important known environmental risk factors have changed over time, including nutritional factors, pollution, chemicals, toxins and infectious diseases in early life. These environmental risk factors might be involved in T1D pathogenesis, as they might initiate autoimmunity or accelerate and precipitate an already ongoing beta cell destruction. In terms of environmental factors, Sardinia is also

particular in terms of the incidence of infection with *Mycobacterium avium paratuberculosis* (MAP) that recent studies have linked to T1D in the Sardinian population. Furthermore, the unique geochemical profile of Sardinia, with its particular density of heavy metals, leads to the assumption that exposure of the Sardinian population to heavy metals could also affect T1D incidence. These factors lead us to hypothesize that T1D incidence in Sardinia may be affected by the exposure to multifactorial agents, such as MAP, common viruses, and heavy metals.

LECT 79

LIPIDOMICS IN PSYCHOPATHOLOGY

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Psychiatric disorders are a burden for society, the health care systems all over the world. This kind of diseases is the plague of the last century. They are usually difficult to treat even if there were a huge improvement in the diagnosis and treatment, and they cause a different type of pain to the patients and their families. Many pathophysiological mechanisms of these pathologies are not fully understood.

In this context, metabolomics could be useful to highlight the mysteries that still surround the brain and its mechanisms in both pathological and physiological states. Indeed, metabolomics is a new “omics” science that, through the analysis of the metabolites present in biological fluids (such as saliva, blood, urine or sweat) or tissues, allows to have a snapshot of the metabolic state of an individual, even in case of drugs administration or in a particular state of health or disease.

Lipidomics is a branch of metabolomics in which lipids represent the focus of the attention. One should not be surprised to see the application of lipidomics for the investigation of the brain, indeed the brain is the organ with the highest percentage of cholesterol and lipids are used as neurotransmitters. Moreover, in recent investigations, fish oil emulsions seem to exert modulatory effects in the neuroinflammation. Cholesterol is fundamental for the neuronal plasticity and synaptic function because of its involvement in the formation of the so-called lipid rafts in the synaptic terminal. Lipid rafts are temporary structures in which the receptors are

disposed of in the most efficient way to the synaptic transmission to occur. Other classes of lipids are involved in these structures, such as sphingomyelins and ceramides. Recent studies linked the lack of cholesterol to different psychiatric disorders and suicide, especially in human males. The reason for this phenomena is thought to be that the lacking of cholesterol may influence the formation of the synaptic lipid rafts, thus in these people, the synaptic transmission is less efficient, especially in the serotonin network which is thought to be involved in mood and behavior regulation.

Another classes of lipids, which seem to be involved in these pathologies, aggression, in particular, are the omega 3 and 6. Investigators tried to administer these lipids to people that display aggressive behavior (even children), and they saw some behavioral improvements. Furthermore, recurrently violent criminals have a low level of lipids in their blood. Moreover, people who experience psychotic experiences at 18 years of age show metabolic abnormalities already at 12 years [1].

Sure these hypotheses are fascinating, and they need further studies to be confirmed, but it could be a new beginning in the understanding of these disorders in order to guarantee tailored treatment to these patients and improve their survival and their quality of life.

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LECT 80

LEONARDO DA VINCI: PAINTER AND ANATOMICAL INVESTIGATOR 500 YEARS LATER

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Leonardo da Vinci was the embodiment of the "Renaissance man", a man who had attained mastery over all branches of art and science. He was

a painter, sculptor, architect, and engineer besides being a scholar in the natural sciences, medicine, and philosophy. At the age of 15, he became an apprentice to the Florentine painter and sculptor Andrea del Verrocchio, the foremost artist of his day, remaining with him until as late as 1480. In 1482, Leonardo moved to Milan in the hope of obtaining the patronage of Ludovico Sforza, also known as Ludovico il Moro. Leonardo offered his services as a military engineer, sculptor, and painter. He would stay in Ludovico's service for 18 years. In the mid- to late-1480s, he seemed to have started on his vast range of scientific studies, dabbling in botany, anatomy, medicine, architecture, military engineering, geography, and many other subjects. We know about his studies from the enormous amount of drawings and sketches that he left behind. In 1499, after the defeat of Ludovico Sforza by the French, Leonardo left Milan. In 1500, he returned to the city of his childhood, Florence. In 1502, he was employed by General Cesare Borgia as an architect and military engineer, with whom he traveled, mainly through Central Italy, studying the terrain and preparing maps for Borgia's future military campaigns. In 1503, Leonardo came back to Florence. He was commissioned by, a friend of Leonardo's father, to paint a portrait of the Francesco del Giocondo wife, Lisa Gherardini. The result was the Mona Lisa (La Gioconda) (1503-1506), which was to become one of the most famous pictures in the world. This portrait was not finished in time and never delivered to the client. From 1506 to 1512, Leonardo lived mostly in Milan under the patronage of Charles D'Amboise, the French governor of the city, also continuing his anatomical studies. After the death of Charles d'Amboise in 1511, Leonardo accepted the protection of Giuliano de Medici, brother of the future Pope Leo X, with whom he then traveled to the papal court in Rome. Leonardo, by now 61 years old, apparently hoped to become a court painter there receiving artistic commissions as those that the Pope had given to Raphael and Michelangelo. In 1515, Leonardo was called to Bologna and commissioned to make a centerpiece for the peace negotiations between the French King Francis I and Pope Leo X. This is where he probably first met the French king, who would go on to become the patron of his later years. In 1516, Leonardo was invited from Francis I to come to the French court. He had a residence in Cloux, close to the King's residence in Amboise. However, his only obligation was to converse with the 22-year old King, who visited him almost daily. Leonardo died

on the 2nd of May, 1519 in Cloux and was buried in the Church of St. Florentine in Amboise. Leonardo's reputation in his lifetime was immense, and his work visibly influenced many contemporary artists.

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LECT 81

CAKUT: THE VALUE OF ULTRASOUNDS

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Congenital anomalies of the kidney and the urinary tract (CAKUT), are the most common anomalies in neonatal age and their early diagnosis prevents the occurrence of chronic diseases affecting these organs. In our experience, the combination of pre- and post-natal sonography allows for a precise diagnosis of the CAKUT. In our Pediatric Radiology Ward, we screen these abnormalities with ultrasounds performed during the neonatal period and a subsequent follow-up [1]. In particular, about the investigations of the hydronephrosis, sonography is performed at birth to evaluate the severity of the dilations and further evaluation by a specialist if it is necessary. In hydroureteronephrosis (dilation of the pelvis, of the kidney goblets and the ureters) and in the obstructive megaureter, that represents the second cause of neonatal hydronephrosis, the renal ultrasound shows the dilation of the ureter often associated with hydronephrosis. The vesicoureteral reflux is investigated by ultrasounds (which represent the first level examination) for morphologic evaluation of the kidney, of the bladder and the urinary tract. In case of multicystic dysplastic kidney, the diagnosis is made by sonography, even in the prenatal period, that shows the cystic alterations in the whole kidney that appears enlarged for the presence of cysts with

subsequent displacement of the functional tissue. The ultrasound examination allows making the diagnosis of the pathology of the number of the kidney. In particular, in the case of unilateral renal agenesis, it is necessary to make a follow-up to evaluate the secondary hypertrophy of the residual kidney. In the case of ectopic kidney, the exact position of the kidney is located by the ultrasound examination and the possible associated alterations. Regarding the ureterocele, the sonographic examination evaluates the possible association with pyeloureteral duplicated collecting system. For the posterior urethral valves, the neonatal sonography usually shows bilateral hydronephrosis and indirect bladder signs of obstruction. On the other hand, for the ectopic ureter, the ultrasound is the first level examination and allows to evaluate the entity of the dilations of the urinary tract and to doubt the ectopia of the ureteral exit.

In conclusion, the congenital malformations of the kidney and the urinary tract have a profound impact with an incidence of 10% of live births and represent one of the most important causes of chronic kidney insufficiency in infancy. This explains the major importance of the renal vesical sonography that is an easily applicable methodology since it does not require any particular preparation and allows for the investigation of the kidney, urinary tract and the bladder (when full).

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LECT 82

CAKUT: THE VALUE OF CLINICS

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Congenital abnormalities of the kidney and urinary tract (CAKUT) are a group of heterogeneous malformations. The incidence is between 0.3 and 1.6 x 1,000 births. CAKUT is relatively common, comprising between 20 and 30% of all malformations diagnosed in the perinatal period and affecting up to 2% of pregnancies. Other malformations are present in 30% of children with CAKUT, and lots of genetic syndromes may include CAKUT: over 500 syndromes including CAKUT have been described. Infants and children with CAKUT have higher probability, compared to healthy peers, of

developing urinary tract infections (UTI). CAKUT have constituted in the recent past 50% of the causes of chronic kidney disease (CKD) in children. Therefore, it is important to the multidisciplinary approach for their accurate diagnosis and therapy. The prognosis in CAKUT is based mainly on two factors: nephron numbers at birth and possible subsequent acquired nephron loss in the next period of life. Nephron numbers at birth depend on: possible preterm birth, unilateral or bilateral involvement and from the presence of kidney dysplasia. After birth, the prognosis is based on the possibility of recognizing and promptly treating UTI, and subsequently, in adulthood of a true lifestyle, with appropriate nutrition, avoiding high blood pressure, obesity, and diabetes. Clearly, in prognosis, we cannot ignore individual genetic differences and the type of CAKUT.

The therapy is almost always medical where is possible, except for cases with precise surgical indications, which are a small part of CAKUT patients. In the clinical approach, it is therefore essential to select patients to undergo surgery, avoiding surgical procedures not indicated. Therefore, the multidisciplinary approach in these patients is crucial.

The primary objective for the neonatologist and pediatrician is to follow guidelines, distinguishing between children with significant CAKUTs and those with CAKUT with a more benign clinical course, avoiding unnecessary investigations and therapies.

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LECT 83

NON-FAMILIAL HEMATURIA

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This lecture aims to give a step by step and evidence-based approach to hematuria in neonates and children. A good history taking and physical exam helps us to narrow the investigation in early steps regardless of being asymptomatic vs. symptomatic,

or gross vs. microscopic, transient vs. persistent, isolated or with proteinuria, and inherited or non-familial.

The dipstick is an easy cheap method to detect blood or Hem in discolored urine. Dipstick screening of school-age children revealed a prevalence of 3.3% for blood in the urine. Urine analysis is mandatory to confirm hematuria that is defined by the presence of more than 3-5 RBC/HPF in the urine. Morphology of RBCs helps to discriminate the source of blood from glomerular or no glomerular. The frequent underlying disease is infection, crystalluria, including hypercalciuria, IgA nephropathy, and thin basement membrane disease.

Interestingly cow's milk allergy has been reported as a benign reason for hematuria in infants. The outcome and treatment depend on the etiology. Rarely, kidney and bladder tumors might early present as microscopic or macroscopic hematuria and always cautiously should be kept in mind. There is sometimes no underlying disease to be detected; in this case, long term follow-up is required to ensure that renal function to be maintained. In conclusion, after taking history and physical exam, a stepwise study recommended for persistent hematuria. If no disease was discovered, besides giving assurance, long term follow-up is suggested.

LECT 84

NEPHROGENIC SYNDROME OF INAPPROPRIATE ANTIDIURESIS

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Nephrogenic Syndrome of Inappropriate Anti-diuresis (NSIAD) is a rare monogenic X-linked disease characterized by a renal deficient water balance regulation. As a result, the inability to dilute urine determines hyponatremia, hyposmolarity, euvoemia, inappropriately concentrated urine, increased natriuresis. In addition, undetectable or very low Arginine-Vasopressin (AVP) circulating levels allow a differential diagnosis with the Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH). In the highest percentage of reports, NSIAD depends on mutations affecting AVP receptor 2 (V2R), with a subsequent gain of function and constitutive activation. The syndrome may occur in single patients or familiar associations,

and hyponatremia can be acute, recurrent, or chronic.

NSIAD typical onset is in neonatal and infantile period, with acute hyponatremia and seizures, but it can occur later in life, with variable symptoms. Patients are generally males, hemizygous for AVPR2 mutation, but females can be affected due to lyonization process. The exact prevalence is difficult to estimate, mostly due to unrecognized or delayed cases, potentially persisting in asymptomatic status. Our research group diagnosed and published the first neonatal-onset case (triggered by fluid overload following perinatal asphyxia). Twelve years later, we also provided an update of neonatal and infantile-onset cases available in the literature, in addition to the novelties regarding physiopathology and prognosis of such disease [1].

Clinical reports of NSIAD are mostly caused by V2R mutation variants R137C/L (arginine-cysteine or -leucine). Moreover, the substitutions F229V (valine-phenylalanine), I130N (isoleucine-asparagine) and L312S (leucine-serine) have been reported [1]. Very recently, a new molecular pattern has been described in a little number of patients, often in association with other endocrine disorders. This new mutation affects the GNAS gene, codifying the G α s stimulatory protein involved in V2R signaling [2-3].

The early diagnosis of NSIAD allows the treatment and prevention of severe hyponatremia episodes, potentially impairing neurological outcome or causing death. Among available treatments, water restriction and urea administration can be performed. In selected cases, Vaptans seem promising. In the case of hyponatremia, high urinary osmolality, increased natriuresis, low plasma osmolality, and sodium levels, NSIAD must be taken into account, and AVP levels should be measured.

Diagnosis is confirmed by genetic testing; in addition, screening in relatives is useful even if asymptomatic. The newly reported findings underline that NSIAD pathophysiology still requires investigation; different mutations could influence clinical manifestations, outcome and therapy response, even if current evidence is not enough to deduce statistically relevant conclusions about genotype and phenotype correlations. We hope that future therapies could be adapted to the patients' features.

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LECT 85

RENAL MANIFESTATIONS OF VASCULITIS IN CHILDREN

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A systemic vasculitis is a group of diseases characterized by inflammation of blood vessels. The size of the vessel affected varies among the different forms of vasculitis. There are three main subgroups: large, medium, and small-vessel vasculitis. Among small vessel vasculitis, the antineutrophil cytoplasmic antibody (ANCA)-associated forms (AAV) are of particular importance. AAV are chronic, often relapsing diseases that can be organ or life-threatening. This subgroup includes: microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg-Strauss) and the form limited to the kidney. ANCA are serum autoantibodies and represent the serological markers of small vessel vasculitis. Renal involvement is present in the majority of patients with AAV and a miss or delayed the diagnosis of renal vasculitis results with life-threatening conditions. Renal biopsy remains the 'gold standard' in diagnosing ANCA-associated glomerulonephritis. The risk of end-stage renal disease and patient survival are closely associated with renal function at presentation. The gold standard for diagnosis remains renal biopsy. Prompt treatment is crucial, and remission can be achieved and maintained in most cases, with a combination of high-dose steroid and immunosuppressive drugs. This therapy has to be continued for at least 24 months after a substantial remission has been obtained because the early cessation of treatment is associated with an increased risk of relapse. For this reason, patients should be regularly monitored in order to promptly diagnose and treat a possible recurrence of AAV.

LECT 86

CLEFT-PALATE-LIPS

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The presentation will address the different issues of craniofacial orthopedics in patients with cleft lip and palate. The orthodontist has relationships with the patient with congenital Cleft-Palate-Lips (CPL) from the first days of life and will treat the patient with oral appliances (obturator plates) that will help the phase of primary surgery. Furthermore, the obturator plates are useful for guiding the growth of bone segments, to allow the tongue to take a more physiological position, for better nutrition. The Orthodontist continues to follow patients with craniofacial orthopedic therapy, which aims to reduce the sequelae of primary surgery and prepare optimal secondary surgery. The therapeutic possibilities are numerous and are based on the use of extraoral tractions, rapid expanders of the maxillary suture, and devices to reposition the mandible and multi-brackets therapy. Clinical cases will be presented with a 20-year follow-up. A review of the reference literature on the clinical procedures will be presented.

LECT 87

THE HEALING WITH MINIMALLY VISIBLE SCAR – OUR THIRTEEN YEARS OF EXPERIENCE WITH NEONATES CLEFT LIP SURGERY

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INTRODUCTION

We present the results of our thirteen years of experience with neonates cleft lip surgery with newborns up to 8 days old.

MATERIAL AND METHODS

We operated on 644 patients cleft lip or cleft lip and palate at the age of 1 to 8 days after birth: 532 neonates with unilateral cleft lip and 112 with a bilateral cleft lip. One surgeon from December

2005 to December 2017 performed all operations. A neonatologist was responsible for preoperative care in the Well Baby Nursery and postoperatively performed 3D scans of palate shaped casting using a laser scanner and FESA method as well as facial scanner 3D. The ENT specialist who evaluated torus tubarius initiated the first phase. Following this, the eardrum was examined, and if present, middle ear fluid was sucked out. We believe this is the earliest detection and treatment of OME. Newborns left the hospital between the 3rd and 4th postoperative day. All patients wore supportive silicon nostril retainers for 2-3 months.

RESULTS

We have experienced only 5 complications resulting from this surgery. At the time of patients' discharge the wounds were usually healed. We presume that the aesthetic results are superior to patients operated in 3 months and later. Comparison of 3D scans of palate and face between the study group and controls revealed no significant difference in maxilla and face growth.

DISCUSSION

Cleft lip surgery is usually performed at the age of 3 months or later. Nursing babies with visible facial disfigurement for three months can adversely affect the psychological wellbeing of these patients' families. By early surgical intervention we achieved not only good anatomical correction but we significantly improved the quality of life of the whole family.

CONCLUSION

If performed under high quality anesthesiological conditions, neonatal, and care settings, and of course with experienced hands, the early correction of cleft lip is a safe method for neonates and gives very good aesthetic results

LECT 88

TONGUE TIE – FROM EMBRYOLOGY TO TREATMENT

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INTRODUCTION

Lingual short frenula can alter the interconnections between the bone bases and the postural control of the tongue, and they can also lead to: anomalous tensions at the level of the hyoid bone; cervical

disorders and postural problems that may affect the tongue. The complications originating from the short frenulum are numerous and heterogeneous as listed below:

- organic differences and language difficulties;
- ineffective latch-on or sucking during breastfeeding;
- severe occlusal deficits.

In the most severe cases, the shortness of the frenulum can generate important complications such as occlusal deficits: delayed eruption of lower incisors; teeth rotation around their longitudinal axes; front pouches that make complete mouth closure impossible; inter-incisive diastemas (large spaces between central incisors); short lingual frenula and swallowing problems.

The most common surgical therapies are: frenotomy and frenectomy.

MATERIALS AND METHODS

Considering the beneficial outcomes of the laser and both the speed and simplicity of its use, we have decided to treat with a diode laser – surgical mode – all those patients with short lingual frenulum or ankyloglossia.

CONCLUSIONS

The laser is an excellent alternative to surgical scissors, as it makes it possible to avoid anesthesia. The operations above are simple and extremely advantageous: not only are they noninvasive, but they also are decisive.

LECT 89

THE ORAL MICROBIOTA: SILENT ENEMY OR NECESSARY BACTERIAL TISSUE?

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ORAL MICROBES AND HUMAN DISEASES

Oral microbe communities have been explored and studied for several decades, and investigations of the role of microorganisms residing in the oral cavity have attracted much attention in these last years, alongside classical human infectious diseases. Numerous studies have reported changes in oral microbiota during not only classical oral bacterial diseases such as periodontitis but also different systemic illnesses. These include: cardiovascular disease, colorectal cancer, rheumatoid arthritis, Alzheimer's disease, as well as cardiovascular infection and adverse pregnancy outcomes. Oral microbiota is

mainly located on the tongue dorsum with about 800 different microbial species, and some of these are periodontal pathogens (PP). The study of these Gram-negative anaerobic bacteria linked with inflammatory processes has attracted the attention of researchers outside the oral field, due to the potential influence of these bacteria on the initiation and/or progression of several systemic degenerative diseases. These bacteria could promote the development of systemic diseases in an indirect way, such as toxin production (i.e., LPS) or directly by blood stream-migration with serial transient bacteremias. These occur in some cases following oral tissue injuries after, for example, surgical procedures. Obviously, bacterial accumulation on the tongue and teeth, due to poor oral hygiene and/or host habit factors, smoking and dietary habits could also cause systemic harm to the host. For example, several PPs evade innate immune detection via Toll-like receptor (TLR)-4, facilitating chronic inflammation in different tissues.

THE OTHER SIDE OF THE COIN: THE PHYSIOLOGICAL FUNCTIONS

On the other hand, some researchers have clarified the commensal-physiological role of some PPs, such as *Fusobacterium nucleatum*. In fact, according to the current experimental hypothesis, this microorganism could be useful in tongue biofilm for modulating the olfactory-taste perception of vegetables. In the same way, they are also able to interact with the bitter taste system implicated in innate immune response defense against respiratory pathogens. In fact, in respiratory ciliated cells, stimulation of these taste receptors, such as T2R38, results in the activation of the innate immune mechanisms, including increased, mucociliary clearance and nitric oxide release.

CONCLUSION

The presence of different commensal-turned pathogen bacteria in oral microbiota could modulate a "double-sided behavior" as a biological function. In this context human habits such as alimentation, from the first day of life, play a crucial role in avoiding oral microbial dysbiosis and consequently, lowering the risk, throughout the life of severe systemic diseases.

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LECT 90

EARLY ORTHODONTIC TREATMENT: WHY, WHEN AND HOW

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INTRODUCTION

The timing of orthodontic interventions has been a contentious topic for many years with early treatment to address or indeed to prevent skeletal discrepancies in all three spatial planes and to alleviate crowding in everyday practice. In terms of effectiveness, however, broadly speaking early intervention is not superior to later intervention.

Pediatricians play an important role in promoting oral health care, and their advice regarding dental procedures or therapies may be strategic. This short review is intended to provide answers for the more common questions that parents and pediatrician may have regarding the oral health of children. The controversies surrounding early orthodontic therapy continue to be areas of discussion. Why does the orthodontist want to initiate orthodontic treatment in a less than a 7-year-old child? These subjects have relevance not only for pediatric patients but also for all people involved in children care as well.

MATERIALS AND METHODS

Many different studies centered on early treatments were taken into account. This systematic review will summarise the evidence Available at randomized controlled trials in order to inform treatment decision making on early orthodontic treatments in pediatric patients.

RESULTS

At the end of this review, different specific treatment priorities were focused in order to avoid worsening of orthodontic diseases with age progression.

Main fields of interest resulted:

- posterior and anterior crossbites;
- space management;
- management of tooth number;
- class II malocclusions;
- class III malocclusion;
- habit control.

A correct early approach in these cases can reduce crowding, mandibular asymmetries, ankylosis, abnormal tooth eruption and dislocation, root damages and resorption, reduced mandibular growth and a series of aesthetic defects that could be easily avoided intercepting a deviated pattern of growth of teeth or facial bones

CONCLUSIONS

Early treatment approach in selected patients and pathologies can ameliorate outcomes in orthodontics. Pediatricians and parents should be

informed in details about treatment possibilities to avoid delay in diagnosis and recovery a normal occlusion as soon as possible.

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LECT 91

NEONATAL CARDIOGENIC SHOCK: WHAT IS RIGHT?

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INTRODUCTION

Although congenital heart disease (CHD) is the most likely cause of neonatal cardiogenic shock, other conditions such as severe persistent pulmonary hypertension of the newborn, myocarditis, myocardial ischemia/infarction, arrhythmias, and metabolic conditions are encountered. Treatment is supportive of reducing end-organ damage and aimed to remove the underlying cause, but balancing the drugs is challenging.

CASE REPORT

We report a case of a preterm neonate born at 30 weeks of gestation, admitted to the Neonatal Intensive Care Unit with severe heart failure leading to cardiogenic shock. His mother followed regular ultrasound scans during pregnancy. During a routine third-trimester ultrasound scan, severe right ventricle hypokinesis and dilation was noted. Given his critical intrauterine condition, delivery was performed. Apgar score was low, and signs of heart failure with severe central cyanosis appeared. Capillary blood gas on admission showed mild respiratory and metabolic acidosis. Postnatal echocardiogram excluded CHD and showed important right ventricle hypokinesis and dilation. Blood pressure (BP) on admission was adequate,

and an electrocardiogram showed sinus rhythm and normal morphology. The baby's condition has deteriorated during the following hours with signs of cardiogenic shock. Fluid resuscitation through an umbilical venous catheter was initiated along with dobutamine and prostaglandin E1. Surfactant was administered, and tracheal intubation was later maintained to reduce the work of breathing. Right ventricle dilation and kinesis progressively worsened, with left ventricle involvement and severe ejection fraction reduction, necessitating higher dobutamine dose and furosemide. Severe lactic metabolic acidosis and poor renal perfusion, as demonstrated by Doppler ultrasound, were present. Dopamine and fenoldopam were given to reach an acceptable renal perfusion, and milrinone was initiated to support myocardial function. His condition has begun to improve slowly since the fourth day of life, leading to gradual discontinuation of drugs. Troponin was elevated since the first day of life, slowly lowering during hospitalization. When clinical stability was reached, a cardiac MRI scan showed focal myocardial lesions.

CONCLUSIONS

Without a diagnosis or waiting for surgical correction in CHD, treatment includes: avoiding of hypoxia, acidosis, hypocalcemia, hypomagnesemia, and hypoglycemia which have a negative inotropic effect, prostaglandin when duct dependent systemic or pulmonary blood flow is present, catecholamines, phosphodiesterase inhibitors, ventilation, and diuretics. Dobutamine has an inotropic effect, increases heart rate, and reduces systemic vascular resistance. Dopamine effects depend on dosage and include an increase in urine output, heart rate, and BP. Inotropes should be carefully used to avoid high myocardial oxygen consumption. Milrinone has both inotropic and vasodilator properties, and as diuretic, furosemide is preferred.

LECT 92

A CHALLENGING CASE OF GASTROESOPHAGEAL REFLUX

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INTRODUCTION

Vascular rings (VRs) are rare malformations representing around 1% of congenital cardiovascular

anomalies, due to abnormal development of the aortic arch complex. They may be asymptomatic or present with respiratory and/or gastrointestinal symptoms that depend on the degree of tightness of the ring and tracheoesophageal compression. Most children with VRs present with symptoms in the first few months of life and require surgery within the first year of life. Symptomatic VRs may require early surgical intervention in order to avoid prolonged severe vascular compression of the airways and serious complications.

CASE REPORT

A 5-month-old child presented to our Pediatric ER with complaints of feeding difficulties, in particular, slow feeding and hyperextension of the head while feeding, and gastro-esophageal reflux. His parents also reported noisy respiration with stridor and, occasionally, apnea and cyanosis. During the physical examination, the patient had stridor and noisy breathing throughout the respiratory phases. The patient underwent a barium esophagography, which showed persistent bilateral indentation of the esophagus. Chest radiography with frontal and lateral views showed a retro-tracheal opacity and tracheal focal stenosis. Therefore, he was admitted to our Pediatrics Ward for further investigations. During hospitalization, he underwent CT-angiography, which highlighted the presence of a double aortic arch encircling the trachea and esophagus. Bronchoscopy confirmed an external compression of the trachea just above the carina, without evidence of tracheomalacia. A comprehensive cardiac evaluation with echocardiography was also performed, which excluded other cardiovascular malformations. Subsequently, the patient was referred to a specialized Surgical Centre in order to plan his therapeutic follow-up.

CONCLUSIONS

VRs represent a challenge for the pediatrician due to the heterogeneity and non-specificity of their clinical manifestations. The diagnosis should be suspected in any infant who presents with symptoms of respiratory distress and should always be considered in the differential diagnosis of all cases of resistant asthma and/or failure to thrive with feeding difficulties.

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LECT 93

A RARE CAUSE OF FAILURE TO THRIVE: DIAGNOSTIC APPROACH AND DISEASE COURSE

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G. is a girl evaluated at 4 years old for failure to thrive and developmental delay. Her medical history showed language delay and exercise intolerance since 3 years old. The physical examination revealed xeroderma, joint hypermobility, muscular hypotrophy, weakness of the lower limbs, hyperreflexia, systolic murmur. The primary pediatric evaluation for growth failure turned out to be negative, except for raised lactate concentration in blood. Aminoacidemia showed increased alanine concentration, reflecting persistent hyperlactatemia. Urine organic acid analysis detected lactic aciduria and Krebs cycle intermediates. A mitochondrial disease was suspected, and in order to establish the diagnosis brain MRI was performed. It showed characteristic T2-weighted bilateral hyperintense lesions in basal ganglia and midbrain, while spectroscopy revealed the presence of lactate and relatively high choline levels. Sequencing of mtDNA identified a pathogenic single nucleotide variant of MTTL2, not maternally inherited and not previously described in the literature. Symptoms, neuroimaging, and mutation were suggestive for Leigh Syndrome (LS). Seizures occurred, but there is no need for therapy. G. had to worsen of neuromuscular symptoms, as reflected in changes in MS-MRI. Muscle biopsy revealed findings suggestive of mitochondrial myopathy such as COX deficiency, abnormal SDH and NADH staining, absence of ragged red fibers. Skeletal muscle respiratory chain testing was not performed because of muscle's scanty. At 5 years old AEP displayed central deafness, so cochlear implantation was recommended. G. requires enteral tube feeding caused by weight decrease. G. assumes Coenzyme Q10 (CoQ10), Riboflavin, Thiamine, Idebenone, Folic acid, Biothine, in order to improve oxidative damage. LS is the most common pediatric presentation of mitochondrial disease. LS is an

early-onset progressive neurodegenerative disease with variable symptoms, caused by defects of mitochondrial oxidative phosphorylation system (OXPHOS) and associated with the development of bilateral symmetrical lesions in basal ganglia and brainstem, which are the hallmark of the disease. LS is genetically highly heterogeneous. Most of the disease's genes encode structural components of the OXPHOS complexes or proteins required for their assembly, stability, and activity. There are possible modes of inheritance, including maternal (for mutations in mtDNA) and autosomal recessive or X-linked (for nuclear-encoded genes). OXPHOS deficiency can lead to hyperlactatemia and increased generation of reactive oxygen species, disturbing intracellular calcium homeostasis, and altered mitochondrial morphology. Tissues that are highly dependent on aerobic metabolism are preferentially involved and undergo to a progressive decline. It is possible to improve the clinical course or delay the progression of LS, partially via the supplementation of specific substrates (CoQ10 and its derivatives, vitamins, pyruvate, dichloroacetate).

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LECT 94

A CASE OF RECURRENT INTESTINAL PSEUDO-OBSTRUCTION

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INTRODUCTION

Primary eosinophilic gastrointestinal diseases (EGIDs) represent a group of disorders that affects the different segments of the gastrointestinal tract and are characterized by eosinophilic inflammation in the absence of known causes for eosinophilia [1]. Non-esophageal EGIDs remain a clinical enigma

with evidence limited to a small number of reported cases. Non eosinophilic esophagitis (Non-EoE) EGIDs might present with different and nonspecific gastrointestinal symptoms depending on involved intestinal tract and extension of eosinophilic inflammation [1].

CLINICAL CASE

A 6-year-old child complained about a clinical history of painful and self-limiting episodes of intestinal distension without any symptoms of intestinal obstruction, constipation or malabsorption. He had no previous history of atopy, abdominal surgery, or chronic diseases. In the last episode, he presented to our Emergency Department with abdominal pain and severe intestinal distension. He had no vomiting, nor diarrhea or constipation. On admission, his vital signs were stable, and he had no fever. Physical examination revealed significant abdomen tenderness and diffuse intestinal meteorism. Laboratory investigation showed a normal blood count with mild peripheral eosinophilia, normal levels of C reactive protein, and no alterations of serum proteins and electrolytes levels. Abdominal X-ray displayed severe distension of the stomach and small intestine without clear air-fluid levels. Abdominal ultrasounds were negative. The patient underwent to upper and lower gastrointestinal endoscopy, showing hyperemic and bleeding colonic mucosa with umbilicated areas of nodular follicular hyperplasia. Histologic findings revealed higher levels of eosinophils/high power field (hpf) in duodenum (> 200/hpf), terminal ileum (142/hpf) and in right colon (97/hpf). Diagnosis of eosinophilic gastroenteritis (EoGE) was made. Therapy with prednisolone and six-food elimination diet was prescribed for 8 weeks with clinical and histological improvement.

CONCLUSION

We described a pediatric case of EoGE characterized by recurrent, severe, and painful abdominal distension mimicking abdominal sub-obstruction. Few cases reports about abdominal obstruction in patients with non-EoE EGIDs are reported in adults [2]. In these cases, diagnosis of muscle involvement required laparoscopy. In children diagnosis of muscle subtype of EGID is very difficult because: a) it is limited to endoscopic biopsies of the mucosal layer, b) disease can mimic other intestinal diseases, c) there is no evidence on the usefulness of non-invasive radiological test. Different gastrointestinal diseases may present with severe and painful abdominal distension in children; however, pediatricians have to consider non-EoE EGIDs in the differential diagnosis.

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LECT 95

A STRANGE NYSTAGMUS: CLINICAL EVALUATION OF "DANCING EYES"

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INTRODUCTION

Involuntary eye movements are not so rare in children, and not always pathologic. It is, therefore, important for pediatricians to learn how to distinguish between benign and alarming eye movements.

CASE REPORT

L., 2 years old, arrived at neurological consultation because of persistent nystagmus (NY) diagnosed by an ophthalmologist some weeks earlier. She presented with rapid, conjugate, multidirectional, intermittent, arrhythmic eye movements, while NY is generally involuntary but rhythmic and repetitive. Our patient's symptomatology was clearly not a NY but an opsoclonus. She also had tongue myoclonus, tremors of the hands, and movement incoordination. Her mother reported disturbed sleep and behavior disorder: irritability, opposition, intolerance towards frustration, and self-harm (she threw herself on the floor and hit her head). The overall symptomatology strongly suggested the diagnosis of Opsoclonus-Myoclonus Syndrome (OMS). We, therefore, admitted L. to hospital, in order to look for the possibly associated neuroblastoma (NB) and to start the treatment. MRI scan of spinal cord pointed out an oval, solid, paraspinal mass about 3 cm in diameter, located left to the first four dorsal vertebrae, that could be an NB. TC scan and scintigraphy confirmed it. Treatment with high dose

prednisone was promptly started and thoracoscopy to remove the tumor was scheduled. The definitive, histologic diagnosis was "ganglioneuroblastoma intermixed variant". L. is now continuing high dose prednisone cycles, according to OMS/DES 2011 protocol.

CONCLUSIONS

OMS – also known as Kinsbourne syndrome or Dancing Eye Syndrome – is a rare neuroinflammatory disease (incidence: 1/5,000,000) of paraneoplastic, parainfectious, or idiopathic origin. The exact pathogenesis is unclear. It typically arises between 1 and 3 years of age. A clinical diagnosis is needed, based on the presence of at least three of the following signs: NB, opsoclonus, movement difficulties with myoclonus and/or ataxia, and behavior/sleep disorder. The neurologic outcome is variable. Motor symptoms can regress or even resolve in approximately 60% of cases, but relapses may occur, e.g., during immunosuppressive treatment withdrawal or intercurrent infections. 60-80% of patients have residual behavioral abnormalities or intellectual disability, that is not improved by prompt therapy and can persist even without motor symptoms. The presence of NB does not seem to influence the prognosis, but NB tumors associated with OMS are characterized by the prevalence of low stage and low-risk disease. OMS should be diagnosed as soon as possible, in order to start the investigation of the possible associated NB and at the same time begin cortisone treatment. Being this mostly a clinical diagnosis, it is fundamental that each physician knows how to recognize the four, typical signs of the disease and, in particular, how to distinguish a simple NY from an opsoclonus (regular oscillation of the eyes vs. rapid, multidirectional, arrhythmic eyes movement).

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LECT 96

IMMUNE SYSTEM OUT OF CONTROL: A CLINICAL CASE ON THE VERGE OF IMMUNODEFICIENCY AND IMMUNE DYSREGULATION

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With the increased availability of high-throughput DNA sequencing, the number of genes associated with inborn errors of immunity (historically named primary immune deficiency disorders [PIDs]) has exponentially increased over the last decade. The most recent PID classification from the International Union of Immunological Sciences includes more than 350 genes, and > 50 of these have been discovered in the last 2 years. In addition to the identification of novel PID-associated genes, it has been recognized that distinct clinical phenotypes may be sustained by Gain of Function (GOF) or Loss of Function (LOF) mutations in the same gene. Finally, various degrees of activity of mutant proteins due to hypomorphic and hypermorphic mutations may also cause PID phenotypic variability. The clinical features of PIDs are broad, ranging from increased susceptibility to infections to significant immune dysregulation, often leading to multiple autoimmune phenomena, including cytopenia and solid organ autoimmunity, in addition to lymphoproliferation and malignancy. The treatment of immune disorders with coexisting immune deficiency and immune dysregulation is challenging, as it requires careful balancing of immunosuppression in subjects at increased risk of infections. In most recent years, the growing ability to define PID pathophysiology at the molecular level has set the basis for the development of targeted therapeutic interventions. New drugs have been developed or repurposed to modulate intracellular pathways whose function is increased or diminished as a result of a specific genetic defect. Such a “precision medicine” approach often permits to selectively target a specific cell function instead of broadly affecting the entire immune system, and may even permit to avoid deleterious side effects on other tissues.

In this context, we are presenting a clinical case of Signal Transducers and Activator of Transcription (STAT) 3 GOF.

STAT3 is activated upon intracellular signaling from type I, II, and III interferons, IL-6, IL10, and IL-21. The original description of heterozygous STAT3 GOF mutations included patients with early-onset autoimmunity or type 1 diabetes in infancy. Experiments based on a luciferase reporter assay have shown that HEK293T cells transfected with a mutant STAT3 had increased transcriptional

activity as compared to cells transfected with wild-type STAT3. Moreover, patients displayed decreased Treg cells and CD4+ T cells that were mainly skewed to the Th1 phenotype. More patients with STAT3 GOF mutations were identified shortly thereafter, expanding the clinical phenotype to non-malignant lymphoproliferation including lymphadenopathy, splenomegaly, and interstitial pneumonia and recurrent infections due to non-tuberculous mycobacteria, fungi, and viruses. Acquired short stature is also a peculiar feature of the disease. Enteropathy and cytopenias were the most common autoimmune manifestations. Attentive studies of these families revealed that there are some genetically affected members with absent or very mild phenotype consistent with incomplete penetrance and variable expressivity. The immunological characteristics of the subject affected by STAT3 GOF germline mutations showed that these patients may suffer from T cell lymphopenia together with an elevated proportion of double negative TCR $\alpha\beta$ + T cells, hypogammaglobulinemia with terminal B cell maturation arrest and a reduced number of circulating dendritic cells, eosinophils, Th17 cells, and natural killer cells. The severe immune dysregulation described in subjects with STAT3 GOF mutations is linked to the well-documented role of STAT3 signaling in promoting inflammation and Th17 cell differentiation and suppressing Treg cells function. Characterization of the molecular abnormalities underlying the disease offered the basis to treat these patients with an IL-6-targeted therapy. Therapy with tocilizumab (an anti-IL6R monoclonal antibody) led to significant improvement of contractures, inflammatory markers, and normalizations of the proportion of Th17 cells in one patient with STAT3 GOF mutation who suffered from severe arthritis and scleroderma-like disease that were refractory to conventional immunosuppressant therapies. Three additional patients did benefit from tocilizumab administration to control autoimmune hepatitis, lymphoproliferation, enteropathy, and interstitial lung disease. Unfortunately, this treatment was not sufficient to completely reverse the immune dysregulation, and Jakinibs had to be added as well. In 3 other patients, tocilizumab and a Jakinib were initiated at the same time, leading to successful regression of manifestations of immune dysregulation. These results support the idea that the combination of IL-6 inhibitors and Jakinib therapy is an effective therapeutic option, and both agents should be considered as a combination therapy in

the treatment of immune dysregulation in patients with STAT3 GOF mutations.

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LECT 97

NEW DIAGNOSTIC POSSIBILITIES FOR NEONATAL SEPSIS

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Neonatal infections remain a major cause of neonatal mortality and morbidity in the world. Early diagnosis and prompt treatment of the newborn with suspected sepsis are essential to prevent severe life-threatening complications. An accurate diagnosis of neonatal sepsis is, however

difficult. Different biochemical markers have been used to differentiate systemic neonatal infection from other non-infectious conditions, but currently, no single ideal biomarker has been identified to accurately diagnose sepsis. With recent advances in medical technologies and, in particular, with the development of multi-omics techniques, several new markers are emerging for the early diagnosis and prediction of the severity of neonatal infections. Due to the difficulties of prompt diagnosis and the high risk of mortality and long-term sequelae, empirical antibiotic therapy is initiated upon clinical suspicion of sepsis. However, empirical therapy is often improperly used. Inappropriate use of antimicrobial therapy is associated with an increasing number of infections with multi-resistant bacterial strains. In the face of the emergence of resistant microorganisms, several laboratories around the world are actively working on the discovery of new antibiotic molecules to replace the depleted pipeline of antibiotic production.

LECT 98

HYPERBILIRUBINEMIA: DIAGNOSIS AND MANAGEMENT

G. Aramouni

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Acute Bilirubin Encephalopathy, although rare, can be devastating, with death or irreversible neurologic sequelae. Unfortunately, it still occurs in 1/70,000 live births in the United States. So, all the efforts, mainly early diagnosis and proper treatment, are essential. Our talk will include some practical cases management according to American Academy of Pediatrics (AAP) practice guideline, quality improvement by reducing Infant Serum Blood Draws, using transcutaneous devices and the discrepancies between TSB and TcB, as well as new treatment devices, in view of its prevention.

LECT 99

(MIS)PERCEPTIONS, METAPHORS, AND STEREOTYPES IN CHILD DEVELOPMENT

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To every great period of Western history corresponds a privileged age of human life (Philippe Aries "Centuries of childhood"). While in the XVII century it was youth, in the XIX century it was childhood, in the XX century it was adolescence. Nowadays, we still focus on adolescence as a key driver for future mental and emotional development. The current presentation will underscore some of the enhancement technologies for children (use of growth hormone, orthodontia, cochlear implant), through the lens of different (mis)perceptions, metaphors, and stereotypes that will potentially influence defining one's identity. We will also show how new technology-related "mental health disorders" such as "nomophobia" (no mobile phone phobia), "technoference" (constant intrusions of technology into everyday life), "cyberchondria" (feeling ill after searching online for the symptoms of illnesses) or selfitis (the obsessive taking of selfies) interfere with so-called "normality" or "normal behavior". We will conclude by saying that while Erikson theory of development focuses on two crises during adolescence (the crisis of identity versus identity confusion and the crisis of intimacy versus isolation), identity development nowadays should be seen in terms of a progressive developmental trend, shaped by values, "appetites" and customs.

LECT 100

SHORT STATURE MANAGEMENT

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Short stature is the most common problem seen in the pediatric endocrinology clinic. The first step in management is to measure these children properly and then to investigate them to look for the causes. Treatment of the cause is the cornerstone. Growth hormone deficiency (GHD) is found in a small percent of these children. Growth hormone (GH) is given successfully in these patients but also approved in several other causes as Turner syndrome, SGA, chronic kidney disease. GH has been given nearly in all diseases associated with short stature like achondroplasia, thalassemia, rheumatoid arthritis, inflammatory bowel disease with variable response. IGF1 is approved in severe igf1 deficiency. Other modalities of treatment

have been tried without definitive conclusions. In this lecture, we will discuss the causes, the investigations needed, and the treatment of short stature, including uses of GH in GHD and other causes of short stature and its safety. Also, we will talk about a few other medications which have been used to enhance the growth in those cases that do not response to GH.

LECT 101

PARTICULARITIES OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA IN THE 5 YEARS FOLLOW-UP OF IASI ONCOLOGY UNIT

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BACKGROUND

While acute lymphoblastic leukemia (ALL) is the most common malignancy during childhood, it also has a high cure rate, with survival at 80-85%. This is a retrospective observational study on the outcome and overall survival of children diagnosed with ALL and treated at a reference center in Northeast Romania.

METHODS

We reviewed the ALL patients aged 0-18 who were admitted to the Pediatric Oncological Department of the "St. Mary" Children's Emergency Hospital Iasi during Jan 2010 - Dec 2014. The patients were treated with multi-agent systemic chemotherapy, according to the Berlin-Frankfurt-Munich (BFM) protocol ALL-2002 and Interfant06. The data collected from the medical records were processed using IBM-SPSS® Statistics 20.

RESULTS

In total, 107 pediatric patients were included in the study. The average age at admission was 6 years and 4 months, with a male to female ratio of 1.8:1. B-cell precursor ALL was diagnosed in 83.12% patients; 12.15% patients had T-cell precursor ALL, and 4.67% suffered from infant leukemia. Bone marrow gene alterations were assessed in 85 cases, namely the mutational status of the BCR-ABL, MLL-AF4, ETV6-RUNX1, E2A-PBX. Thus, 12.15% of patients exhibited ETV6-RUNX1 fusion, 2.80% showed E2A-PBX fusion, another 2.80%

featured BCR-ABL fusion, and 1.87% of them presented MLL-AF4 fusion. Complete remission rate was achieved in 81.3% of cases. The overall mortality rate during induction phase was 6.54%. Overall relapse was at 11.21% and 4.67% in the high-risk group (n = 27). In the latter, the survival rate was 12.15%. The overall survival rates at 1 and then 5-years were 89.72% and 76.64%, respectively.

CONCLUSIONS

The epidemiology, clinical features, immunophenotype, and molecular characteristics we identified in our patients with ALL are similar to those found in high-income countries. The 5-year survival rate in our center is consistent with similar reports from other middle-income countries, yet still lower than in the developed world.

LECT 102

HOW PHYTOTHERAPY COULD HELP PAEDIATRICIANS

M. Biagi

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Phytotherapy is officially defined by the World Health Organization (WHO), the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) as a medical discipline that uses medicinal plants and their preparations for therapeutic purposes: no distinction within official medicine, only the peculiarity of using a "phytochemical" instead of a monomolecular drug. Despite this, a recent survey conducted by the Italian Society of Phytotherapy (S.I.Fit.) showed that not only consumers but also a large number of physicians think that phytotherapy means a safer natural alternative to synthetic drugs; it is rarely confused with homeopathy, more often assimilated to naturopathy. The confusion that arises talking about phytotherapy derives from the not homogeneity of the herbal products that are marketed and used in our country. In fact, alongside the conventionally registered herbal medicines, today tens of thousands of food supplements, cosmetics and other para pharmaceuticals containing extracts and vegetable preparations are on the market. Some herbal food supplements or cosmetics contain formulations and raw materials that are clearly similar to registered drugs and they are on the market in an "alternative" form only for registration simplification and

enormous economic savings, not having to comply with strict pharmaceutical controls; more often, herbal para pharmaceuticals contain formulations that have no quality, no scientific rationale, and are proposed as a pure commercial proposal, following the increasing interest "green style". The latter is a common case in the scenario of pediatric herbal products: thus, pediatricians should be constantly trained and updated as regards phytotherapy, bearing in mind that herbal products, if well and rationally used, have evident therapeutic and health potentialities.

LECT 103

PHYTOTHERAPY IN THE FIRST 1,000 DAYS OF LIFE AND BEYOND

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The time that extends between a woman's pregnancy and her child's second birthday – the first 1,000 days – is considered a unique and critical "window of opportunity"; what happens in this period affects the health and well-being of the future child even decades later. A healthy lifestyle, a correct and adequate diet, including micronutrients during pregnancy and lactation as well as for early childhood, breastfeeding, vitamin and mineral supplementation and optimal and balanced weaning are fundamental elements for harmonious and healthy development. Infants and young children are physiologically more vulnerable to specific adverse effects of herbs than are adults, the peculiarities of the developmental age make them different in terms of absorption, distribution, metabolism, and excretion of some substances, the relatively greater liver size favors more effective detoxification. However, the incomplete maturation of the nervous and immune system could make them more sensitive to the adverse effects of phytotherapeutic remedies, including allergic reactions. Besides, it is appropriate and prudent to consider the limit and potential of phytotherapeutic treatment, its adequacy, the possibility of synergistic effects (phytochemical associations) and interactions with synthetic drugs. Phytotherapy is a medical discipline that involves the scientific use of medicinal plants in therapy that has proven to be good for maintaining good health, preventing frequent functional disorders and for treating various symptoms and diseases,

according to recognized standards of quality, safety, and efficacy. It is distinguished by the use of extracts and products derived from medicinal plants that contain more active ingredients. The WHO considers medicinal plant each plant that contains, in one or more of its organs, substances that can be used for therapeutic purposes or estimates, or which are precursors of chemo-pharmaceutical synthesis. Phytotherapy is the science-based medicinal use of plants and preparations derived from them that has proven to be good for maintaining good health, preventing frequent functional disorders and for treating various symptoms and diseases, according to recognized standards of quality, safety, and efficacy. More parents look to pediatricians for advice concerning the safety and efficacy of herbal products for children. Physicians must keep their knowledge and skills in phytotherapy up to date by regularly participating in learning activities that develop their skills and performance. They must treat and educate their patients on a reasoned use of plant extracts, in line with current tests and research in order to better serve the patient and the profession as a whole.

LECT 104

COLDS AND COUGHS IN CHILDREN

G. Trapani

Family Pediatrician, Sanremo, Italy

The most common pathologies affecting the daily work of the Family Pediatrician are colds and coughs. We now examine the herbal medicinal products used in these infectious diseases. Pelargonium sidoides. The examination of scientific literature shows that EPs 7630 extract of Pelargonium sidoides (Ps) is effective in treating respiratory tract infections with an indirect and mediated effect. From a clinical point of view, it shows a very complete and pleiotropic mechanism of action, due to its rich phytocomplex, which has immune-modulating, antibacterial, antiviral, and ciliary mobility actions, and it can be used to treat the most common respiratory tract infections with good safety and tolerability profile. The "Ps extract for treating acute respiratory tract infections" review, published by the *Cochrane* Collaboration, shows that adequate studies have been published, according to which EPs 7630 extract can be used to alleviate the symptoms of acute rhinosinusitis and the common cold. The extract can be useful in improving

symptoms of acute bronchitis, both in adults and children.

A recent review highlights that EPs 7630 is an efficacious, safe, and well-tolerated herbal medicine in the management of acute respiratory tract infections such as acute bronchitis, acute rhinosinusitis, and acute tonsillitis and pharyngitis in children, adolescents, and adults. Its safety profile remains high, even when used to treat very young children and in any case over 24 months of age. Recent data demonstrate that EPs 7630 is efficacious in children < 6 years suffering from acute bronchitis. This analysis also supports the effectiveness of the product in acute tonsillopharyngitis and acute rhinosinusitis in pediatric age. The use of EPs 7630, common in many European countries (with millions of doses administered per year), maybe related to few reported allergic skin reactions (34 cases), which were quite mild. No safety concerns were identified. Piantaggine (*Plantago major*) is used for the antiviral antibacterial, anti-inflammatory action in coughs and bronchitis. It is also useful in allergy, and it increases the production of lymphocytes and Interferon γ . Elicriso (*Helichrysum italicum*) contains flavonoids with antispasmodic and anti-inflammatory action. Timo (*Thymus s.*): it contains essential oils and thymol which have sedative action in cough and asthma. Rosolaccio (*Papaver rhoeas*) contains alkaloids used in cough and asthma.

LECT 105

PHYTOTHERAPY FOR SKIN DISEASES

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In pediatric dermatology, phytotherapy, used both for local and systemic use, finds an extremely interesting space for intervention. Its field of action ranges from infected dermatitis to atopic dermatitis. It is also important the action of phytotherapeutics in dermal lesions, both primary (cutting wounds or similar) and secondary ones (see scratching lesions). *Cardiospermum* is indicated in infected dermatitis due to its antimicrobial and anti-inflammatory activity due to chlorogenic acid and apigenin. It can be associated with *Calendula officinalis*, always used locally, for its antimicrobial action due to oleanic acid and its anti-inflammatory action due to some calendulaglycoside compounds. In case of wounds, Aloe gel is also indicated for its

pain-relieving activity due to the anti-inflammatory action of the veracylglycan B and C glycans and especially due to the action of the glycoprotein verectin, which also promotes healing by promoting the local microcirculation. It can be associated with *Chamomilla Matricaria*, used locally, for its anti-inflammatory action due to chamazulene. Scarring is favored not only by *Calendula* but also by Aloe gel, whose healing activity is proven. In the case of atopic dermatitis, the main remedy is *Cardiospermum*, which associates an antiallergic action due to apigenin to a specific anti-inflammatory action. Also, finally, orally, associate *Chamomilla* for its anxiolytic action, which is performed through apigenin, which is capable of binding to benzodiazepine receptors.

LECT 106

WHEN TO CHOOSE HERBAL REMEDIES FOR THE TREATMENT OF URINARY TRACT INFECTIONS (UTI) IN CHILDREN. FOCUS ON CRANBERRY

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Urinary tract infections (UTIs), represent the second cause of pediatric bacterial infections, after those affecting the respiratory system. It is estimated that by the age of 16 years, 1/30 male and 1/10 female, may have a UTI. In 30-50% of cases, UTIs are recurrent, especially in subjects with vesicoureteral reflux (VUR), neurological bladder, previous cystitis or pyelonephritis, and malformative uropathy. In 15% of subjects who have had UTIs, arterial hypertension occurs in adulthood. To prevent this complication and to avoid the formation of scars on the renal parenchyma, antibiotic prophylaxis is frequently used in common practice, especially in subjects with VUR, although literature data do not completely agree on the usefulness of this treatment. In this regard, both the physical and psychological impact of a chronic therapy in pediatric age and on his family, the economic costs and, above all, the growing phenomenon of antibiotic resistance, must be considered. That being said, numerous studies have also considered the use of other treatments to prevent recurrent UTIs and the possible related damages: from circumcision in males to the administration of probiotics, vitamins and plant extracts such as Cranberry (*Vaccinium*

macrocarpon). Focusing attention on the latter, also known as American Cranberry, it is evident that the berries of this plant have a centuries-old tradition of use, for the treatment of different clinical situations, including UTIs, before the advent of antibiotics. The main components of the Cranberry phytocomplex are flavonoids (mainly anthocyanidins), catechins, carbohydrates, mineral salts, and tannins; among these, proanthocyanidins of type A are characteristic. These are due to the ability to inhibit the adhesion of *E. coli* fimbriate (type 1 and type P) to the cells of the bladder wall and the subsequent rise in the urinary tract, up to the renal parenchyma. Considering that *E. coli* is the main etiologic agent of UTIs, researchers' interest in Cranberry appears evident. Recent studies conducted in pediatric subjects suffering from UTI have shown that the administration of Cranberry is able to reduce the number of episodes of UTI in male subjects who are not circumcised and can have beneficial effects against the growth of pathogenic Gram-negative bacteria; the preventive effect against UTIs, was found to be higher than the same circumcision in circumcised subjects. Other studies have highlighted the efficacy in preventing UTIs in healthy subjects and efficacy similar to that of antibiotic therapy in subjects with abnormalities of the urogenital system. Considering the number of cases evaluated and the different formulations of Cranberry used in the studies examined, further clinical confirmation is required in terms of efficacy and safety.

LECT 107

HERBAL REMEDIES FOR THE TREATMENT OF SLEEP DISORDERS IN CHILDREN

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It has been calculated that, in the Western world, 25% of children under the age of six suffer from sleep disorders, a percentage that falls to 10-12% from six years of adolescence. To date, there are no drugs approved by either the FDA or the EMA for pediatric insomnia and behavioral techniques remain the first line of treatment. However, many herbal drugs can improve the quality of sleep, including *Chamomile Matricaria* capable of binding to benzodiazepine receptors thanks to a component of the phytocomplex, apigenin. The same sedative

and anxiolytic action demonstrate the Tiglio (*Tilia Tomentosa*), binding to benzodiazepine receptors through a flavonoid active principle. Also, *Melissa Officinalis* has recently shown to possess flavonoids, with anticonvulsant, anxiolytic and moderately hypnogenic effects, able to bind to benzodiazepine receptors, the decrease in anxiety is due to the increase of GABA inhibitory transmitters due to inhibition of the GABA enzyme - transaminase caused by rosmarinic acid, oleanic acid, and ursolic acid. The biological activity of *Passiflora Incarnata* seems to be expressed through inhibition of the binding of 3H-GABA to the GABA receptor with consequent sedative, anxiolytic, and spasmolytic action. Californian *Eschscholzia* (California poppy) demonstrates mildly anxiolytic/hypo-inducing activity by acting on GABA receptors, thanks to the alkaloids contained in its phytocomplex, as demonstrated *in vitro* on rat brain.

LECT 108

EVALUATION SCORE OF THE PARENTAL COMPETENCY IN NEONATAL INTENSIVE CARE UNITS

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The Neonatal Intensive Care Units (NICUs) represents for the parents of the little patients a high emotional impact, characterized by a long-term hospitalization and by high-complexity assistance. These two peculiarities make it fundamental the presence and the active involvement of the parental figure. Then, the discharge is always a challenge for these parents and a moment of high anxiety and concern. Thus, for this reason, it is essential to evaluate the actual ability of the parents to take care of neonates with special needs from a medical and nursing point of view. There are several validated scores to assess these competencies. While there are fewer tools to investigate the perception of the parents themselves concerning their efficacy. Among them, the Perceived Maternal Parenting Self-Efficacy Questionnaire (PMP S-E), which is a self-report questionnaire that measures the maternal self-efficacy, specifically in the context of NICU. Its use is advantageous both for the mothers and the healthcare professionals, as a support in the building of parental empowerment. This study has the aim to describe and analyze this tool, to implement its

knowledge, contributing to keeping up with the continuous transition of the nurse assistance.

LECT 109

PRETERM BIRTH REPRESENTS A TRAUMATIC EVENT IN A CRITICAL PERIOD FOR THE DEVELOPMENT OF THE NERVOUS SYSTEM

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Preterm birth can affect infant mental health. Despite this area being mostly unexplored compared to others, children that are born prematurely seems to be at higher psychopathological risk compared to children born at term. The intervention will be focused on some psychopathological outcomes of the preterm birth, such as: anxiety-depression disorder and withdrawal, temperamental issues, eating disorders. The intervention of the psychologist is located inside a multi-professional healthcare team where, despite the operators proceeding separately in the definition of the medical and psychological aspect, the teamwork retrieves the possibility to analyze the patient's situation in terms of complexity.

LECT 110

THE SKIN OF CRITICAL NEWBORN, BETWEEN EVIDENCE AND GOOD PRACTICE

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The preservation of the integrity of the skin represents a priority in nursing research and an indicator of the quality of the assistance itself. Newborns, especially if preterm, present relevant risk factors for the development of pressure lesions. The prevention and all the procedures performed to protect the skin, are of fundamental importance to preserve the health of these little patients. To detect a lesion is not enough. The knowledge of the reparation and skin maturation mechanisms, the tools for risk's assessment, the advanced medications for each type of lesions and the prevention's procedure to perform in case of lesions occurrence, makes the assistance efficacious. In the course of the research, for the elaboration of the good nursing practices

concerning the management of the skin, interesting foods for though have emerged concerning some assistive aspects. To date, the administered cares are not homogeneous and are mostly based on habits and experience and not on evidence of efficacy. The document aims to uniform these procedures for better efficacy of the treatments.

LECT 111

THE ITALIAN NEONATOLOGY NURSE TODAY

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In the last ten years, the Italian neonatology nurse has been in the middle of an in-depth process of evolution: the assistance course and the operative protocols have been changing, just as much as the organizational models used in operative units. Today, it seems to be more and more evident that the technical component alone is not sufficient anymore to give an exhaustive assistance response in terms of adequacy. This is already detected from the university education where the challenge seems to be. Finally, the individuation of the medical-nursing assistance not only addresses the neonate but also involves the family unit. In this context, the role and the centrality of the neonatology nurses stand out, as they are responsible for the assistance to the physiological and pathological neonate. On the wave of these virtuous changes, in 2018 the Italian Society of Neonatal Nursing (SIN INF) was born, a scientific context able to associate a community of professionals, ideas and experiences. A very ambitious project that aims to converge the attention and the efforts towards the nurse research, the technical-scientific education of the professionals, and the diffusion of the best practices in neonatology. The future aim will be to ensure that this new reality represents the most influential scientific reference for the neonatology nurse in Italy, contributing, furthermore, to standardize the assistance processes that today appear to be widely diversified from the North to the South of the country.

LECT 112

UPDATE ON PATHOGENESIS & MANAGEMENT OF KAWASAKI SYNDROME (DISEASE)

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Professor Kawasaki from Japan first described Kawasaki disease around fifty years ago, and though much research has been done in this field, and many pathogenetic theories have been postulated; still no definite causative agents have been defined. Recently, there has been much research about the genetic predisposition for Kawasaki disease. The classic clinical presentation of Kawasaki syndrome has been more or less the same since it was first described, but, more recently, the description of atypical or incomplete cases has changed the approach to diagnosing this disease. Managing Kawasaki syndrome has passed through a few developments, and the main aim of management is preventing long term complications, mainly the development of coronary artery aneurysms. Recently, the use of steroids for cases not responding to human IgG has been investigated and suggested. The prediction of non-responders might be linked to genetic predisposition in addition to other scoring criteria.

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LECT 113

DONKEY MILK: A NEW PERSPECTIVE FOR HEALTH OF CHILDREN

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The donkey (*Equus Asinus*) is a member of the horse family. Furthermore, until the beginning of the 20th century, it was meant for the feeding of orphan infants, unhealthy children, and the elderly. At present, the consumers' interest in donkey milk (DM) is increasing, and this product is gaining importance and international acceptance. Compared with ruminant's milk, DM has been studied less in the past, but in the last years, research interest and capital investment in DM enhanced.

Milk from monogastric animals, rather than from ruminants, has been suggested to be more suitable for human nutrition based on their physicochemical properties [1]. The protein composition is significantly different from cow's milk: the total content is lower (1.5-1.8 g/100 g) and like that of human; this condition avoids an excessive renal load of solute. The main difference is the proportion of whey proteins: they are 35-50% of the nitrogen fraction while they represent only 20% in cow's milk. This may contribute towards explaining the less allergenic properties of DM and its greater digestibility. Furthermore, the high lactose content of DM confers excellent palatability. Not only its protein but also its lipid fractions showed substantial similarity to that of human milk (HM) [2, 3]. DM has an n-3 PUFA content equivalent to HM and is high in content of lysozyme which, together with immunoglobulins, lactoferrin, and lactoperoxidase, exerts both an immunoregulatory and anti-tumor activity, and it may also act on the digestive tract by reducing the incidence of gastrointestinal infections. It has been recently demonstrated in murine models that supplementation of the basal diet with DM decreases the accumulation of body lipids and affects glucose and lipid metabolism in a manner more like HM than cow milk [4] These biological effects resulted comparable with those elicited by HM [5]. Based on these considerations, not surprisingly, DM was considered as an alternative ingredient in the "solid food-based diet"

or after the first year of life in sensitive infants. Previous studies observed on children affected by cow milk protein allergy that DM was highly tolerated [6] Throughout time, it was confirmed that DM feeding could offer a great solution for the treatment of the most complicated cases of multiple food intolerances in young children affected by a cow milk allergy. The high content of ω -3 fatty acids supports the use of DM as an effective functional food, in the prevention of cardiovascular diseases, and chronic inflammatory processes; in addition, the high percentage of medium and short-chain fatty acids potentiates the antioxidant properties of this milk. Both colostrum and milk from donkey could be useful in the treatment of human immune-related diseases. It may be helpful in the prevention of atherosclerosis, in view of strong vasodilatory and antimicrobial properties. Pathogens and/or their products may play a proatherogenic role [6-8]. Furthermore, based on the above data, our group speculated that DM could be more suitable than bovine milk (BM) to be an ingredient of a HM fortifier for VLBW infants and preterm newborns. Our study is the first randomized, controlled, single-blind clinical trial that investigates the use of DM-derived HM fortifier (DF) for the nutrition of very preterm and VLBW newborns to assess the effects on feeding tolerance of a DF respect to BM-derived HM fortifier (BF). All newborns received HM exclusively (raw own mother's milk or pasteurized donor milk), without any preterm bovine formula supplementation. We observed a lower number of failures (necrotizing enterocolitis, at least 1 episode of feeding intolerance, or death) and a lower hazard of feeding intolerance episodes in the DF-arm. The mean number of episodes per newborn of feeding intolerance, feeding interruptions (any duration), bilious gastric residuals, and vomiting during the observation period was consistently lower in DF-arm. Overall, these results suggest the favorable effect of the DF on feeding tolerance, and we speculate that the quality of DM protein could be responsible for this result, the 2 diets being isoproteic and isocaloric. To conclude, our data may constitute a sound basis on which to plan a further trial with enough power to confirm the higher tolerability of the DF and open new perspectives for the production of HM fortifiers other than those derived from BM [9].

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LECT 114

STRATEGIES TO REDUCE MEDICATION ERRORS IN THE NICU

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The issue of pharmacological errors is of considerable relevance in the pediatric field. However, the data concerning the real incidence of medical errors in the pediatric population are very sparse and inconsistent. Some studies report an incidence of therapeutic errors equal to the adult

population (5.5% of therapeutic interventions) [1], while others recorded a much higher incidence, up to three times higher in children than in adults (15% of therapeutic interventions) [2]. Undoubtedly, preventable adverse drug events in pediatric patients result in severe complications and/or death more frequently than in adults [3]. All the studies agree that, among pediatric patients, newborn infants, in particular the ones admitted to Neonatal Intensive Care Units, are at greatest risk of medical errors and preventable adverse events [1, 2, 4].

Several reports suggest that the use of the computerized chart with a computerized physician order entry (CPOE) and bar code medication administration (BCMA) systems are able to significantly reduce prescription, preparation and administration errors [5, 6]. However, two recent meta-analyses have shown that most of the studies concerning the use of computerized systems aimed at reducing medical error in the pediatric setting do not have a controlled design with a prospective pre- and post-intervention phase and with adequate detection of errors [7, 8]. Therefore, the evidence that these techniques actually reduce the incidence of therapeutic errors and preventable adverse events is limited and more data are required.

In our unit a computerized charting, Neocare, has been implemented. Neocare is a medical-nursing record that interfaces with the services of the hospital, where all the processes in the different departments are fully computerized. The Neocare charting allows to manage the newborn's hospitalization data (personal data, feeding, procedures, diagnostic tests and therapeutic process). The possibility of managing drug therapy through Neocare is conceived and developed in order to limit medical errors, and the clinical risk associated with drug therapy. The system allows, in fact, to carry out a control and a traceability in every phase of the therapeutic process (prescription, preparation, administration). We are currently conducting a prospective analysis of the benefits of introducing a COPE and BCMA system in our Neonatal Intensive Care Unit.

DECLARATION OF INTEREST

G. Como is Neocare Specialist, GPI S.p.A., Trento, Italy.

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