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Lectures

Selected Lectures of the Congress of Pediatrics

CAGLIARI (ITALY) · OCTOBER 25TH, 2024

The Congress of Pediatrics is a Satellite Meeting of the 20th International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 23rd-26th, 2024.

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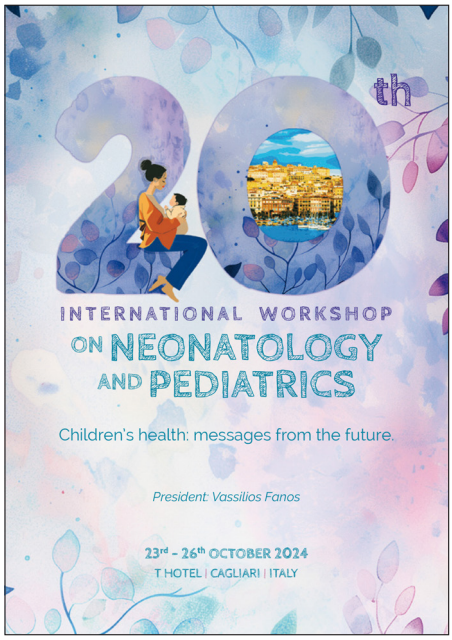

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LECT 1

TH2 INFLAMMATION AND INBORN ERRORS OF IMMUNITY (IEI): AN EVER-EXPANDING UNIVERSE. FOCUS ON *STAT6* GAIN-OF-FUNCTION MUTATIONS

I. Taietti, R. Castagnoli, A. Licari, G.L. Marseglia

Pediatrics Unit, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy

Pediatrics Clinic, Foundation IRCCS Polyclinic San Matteo, Pavia, Italy

Recent evidence suggests that even common allergic symptoms may represent the expression of an underlying inborn error of immunity (IEI) with immune dysregulation, defined as primary atopic disorder (PAD). One of the most recent monogenic PAD to be identified is represented by gain-of-function (GOF) mutations in *STAT6* (signal transducer and activator of transcription 6). To date, 22 patients are reported. Autosomal dominant inheritance has been documented, although *de novo* mutations are also described.

STAT6 is the primary transcription factor that mediates the biological effects of IL-4 and IL-13, playing a critical role in type 2 immunity. For this reason, dysregulation of this axis plays a pathogenic role in various allergic diseases, as dominant heterozygous pathogenic variants of *STAT6* lead to an alteration of the common mechanism of immune dysregulation linked to JAK-STAT.

Most mutations are located in the DNA-binding domain, while mutations in the linker domain, the SH2 domain, and near the Y641 residue necessary for dimerization have been described. These GOF variants can result in both cytokine independence and aberrant transcription.

The main clinical features include:

- severe early-onset atopic disease in all patients: recalcitrant eczematous dermatitis, food or drug allergies, asthma, and severe or recurrent anaphylaxis, with markedly elevated serum immunoglobulin E (IgE) levels and hypereosinophilia;
- gastrointestinal symptoms (75%), frequently including severe eosinophilic gastrointestinal inflammation and, less commonly, diarrhea or protein-losing enteropathy in one family;
- mild recurrent skin and respiratory infections (50%);
- skeletal abnormalities mimicking those observed in autosomal dominant hyper-IgE syndrome caused by heterozygous *STAT3* mutations (osteoporosis, pathological fractures, joint hyperextensibility, and/or vascular abnormalities) (33%);
- short stature (40%);
- significant lymphadenopathy, large polypoid intestinal nodules, and recurrent B-cell lymphomas (e.g., follicular lymphoma) have also been reported.

T-helper 2 (TH2) cytokine-secreting T cells (IL-4, IL-5, and IL-13) are significantly expanded, and TH2 cell markers, including GATA3 and IL4R-α, show increased expression, with elevated serum IL-4 levels. The predominant absence of severe invasive infections or candidiasis is linked to normal expression of TH1 and TH17 cell markers by effector and regulatory T cells.

Therapeutic approaches for this immune disorder include JAK inhibitors (ruxolitinib and tofacitinib) and the anti-IL-4/IL-13 monoclonal antibody directed against IL-4Rα (dupilumab). Both classes of drugs have led to clinical improvement in patients unresponsive to corticosteroids, topical tacrolimus, oral methotrexate, and the anti-IL-5 monoclonal antibody (mepolizumab).

Even in the face of this newly defined condition, genetic analysis remains crucial in the field of clinical immunology, especially in this recently expanding group of IEI. The therapeutic implications will be significant, increasingly pursuing personalized medicine in the field of allergic diseases.

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LECT 2

ANTIBIOTICS AND PROBIOTICS: WHEN TO USE THEM TOGETHER IN PEDIATRICS

S. Esposito

University of Parma, Parma, Italy
Pediatric Clinic, University Hospital of Parma, Parma, Italy

Antibiotics are commonly prescribed in pediatric care to treat bacterial infections, but their indiscriminate use can disrupt the gut microbiome, leading to dysbiosis, gastrointestinal issues, and increased susceptibility to future infections. Probiotics have emerged as a complementary therapy to restore microbial balance during or after antibiotic treatment. The combined use of antibiotics and probiotics in pediatric care aims to mitigate the adverse effects of antibiotics, particularly antibiotic-associated diarrhea (AAD), and support immune system development. The judicious use of probiotics during antibiotic therapy is supported by studies indicating their efficacy in reducing the incidence and severity of AAD, as well as in restoring healthy gut flora. Specific strains of probiotics, such as *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii*, have shown particular promise in pediatric populations. However, the use of probiotics should be tailored to individual pediatric patients, considering factors such as age, type of infection, type of antibiotic, and the child's overall health status. Furthermore, not all probiotics are equally effective, and evidence for the use of certain strains remains limited. In conclusion, the simultaneous use of antibiotics and probiotics in pediatrics can offer protective benefits against the side effects of antibiotics, particularly in maintaining gut health. However, their combined use should be based on clinical guidelines, appropriate strain selection, and careful patient assessment to ensure safety and maximize therapeutic outcomes. Further research is warranted to optimize probiotic strains and protocols in pediatric populations.

LECT 3

THE LONG-TERM FOLLOW-UP OF PRETERM INFANTS

M. Agosti

Neonatology and Neonatal Intensive Care Unit, Mother and Child Department, University of Insubria, Varese, Italy

The follow-up of preterm infants has always been an integral part of the activity in Neonatal Intensive Care Units (NICUs). Prematurity is not a sporadic event but a chronic condition that may manifest more severely over time, especially in cases of extremely premature births. The complexity of infants discharged from our NICUs has made multidisciplinary follow-up services increasingly necessary, integrated with Infant Neuropsychiatry Services and Family Pediatricians. Care cannot end at the moment of discharge; it must necessarily continue over time with the young patients and their families. It is therefore essential to have a shared protocol for managing infants after discharge and to organize follow-up services as uniformly as possible at the national level. Consequently, the care provided to premature and/or at-risk infants during the acute phase in NICUs must continue after discharge through follow-up services and programs aimed at the early identification of developmental anomalies and the implementation of individualized early interventions. The ultimate goal is to improve the quality of life of both the children and their families. In this way, follow-up for at-risk infants becomes an essential step in the continuation of care after the discharge of the ill newborn, particularly for neuropsychiatric issues related to neurocognitive and motor development. It is crucial to identify the numerous potential difficulties in this category of children, whether motor, linguistic, or emotional-behavioral, to ensure early intervention in collaboration with specific local services. Currently, there is a clear indication for extending the timeframe for follow-up evaluations beyond the first 3 years of life, up to 6 years of age. It is well-known that evaluations up to 3 years of age, as currently done by most Italian follow-up programs, primarily detect major disabilities. However, to identify minor anomalies (motor, cognitive, behavioral), evaluations must be extended at least until the beginning of school age. Additionally, literature data on the temporal progression of outcomes in preterm infants have shown a lower prevalence of severe motor outcomes like cerebral palsy and severe cognitive deficits, while neurodevelopmental disorders (behavioral, social competence issues, school learning difficulties, and executive function deficits) are becoming more frequent and manifest later in childhood. These therefore require long-

term follow-up, at least until 6-7 years of age. The continuation of care after NICU discharge, the assessment of both short- and long-term clinical outcomes, early interventions, and the analysis of the long-term effectiveness of new therapeutic-care approaches in managing preterm infants in NICUs represent the main objectives of follow-up programs. These define a new clinical frontier, closely linked to clinical research, not only for Neonatology Departments and NICUs but also for all Maternal and Child Departments in hospitals and local health services.

LECT 4

LOW DOSE MEDICINE AND RECURRENT RESPIRATORY INFECTIONS: A DELPHI CONSENSUS SURVEY

G. Bona[1], M. Agosti[2], A. Arrighi[3], S. Bernasconi[4], G. Ciprandi[5], S. Leonardi[6], G.L. Marseglia[7,8]

[1]*Department of Health Sciences, University of Eastern Piedmont, Novara, Italy*

[2]*Pediatric Department, Hospital "F. Del Ponte", University of Insubria, Varese, Italy*

[3]*Pediatric Primary Care, ASL 8, Arezzo, Italy*

[4]*"Complementary Medicines and Integrated Therapies" study group of the Italian Pediatric Society (Società Italiana di Pediatria – SIP)*

[5]*Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy*

[6]*Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy*

[7]*Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, Pavia, Italy*

[8]*Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy*

Recurrent respiratory infections (RRIs) are a common problem in childhood. The social and economic impact of RRIs is global, requiring frequent medical care and often resulting in the prescription of inappropriate or unvalidated treatments. Although the etiological agents are not always detected, viruses constitute the common cause of infections. Despite their frequently benign course, the real challenge for pediatricians is to differentiate which conditions need thorough diagnostic assessments and specific treatments.

Regarding the possible preventive treatment of RRIs, a previous Inter-society Consensus reported that only one lysate bacterial extract and pidotimod had weak positive recommendations for selected subjects [1]. Nevertheless, many pediatricians use immunomodulators in real-world practice to offer a solution to parents who need help with their children's health problems.

In this scenario, Low-Dose Pharmacology might represent a new possible solution. Low-Dose Pharmacology is based mainly on administering physiologically low doses of signaling molecules (cytokines, hormones, neuropeptides, and growth factors) orally, which act at their physiological working range between micrograms and femtograms.

Since 2009, preclinical and clinical research have shown the effectiveness and safety of Low-Dose Pharmacology [2]. Citomix™ is a multicomponent low-dose medication for oral administration that contains herbals, substances of animal origin, and signaling molecules.

Based on this background, a Delphi Consensus on managing RRIs using this medication asked a large group of Italian primary care pediatricians (Consensus Panel), deeply involved in managing children with RRIs, to express their agreement grade for each statement [3]. Consensus was achieved based on the agreement of at least 66.6% of the Consensus Panel. The 18 statements concerned RRI definitions and RRI management using multicomponent low-dose medication. The statements regarding the RRI definitions reached high levels of agreement, with consensus ranging from 92.0% to 98.2%. Also, the statements regarding RRI treatment and prevention showed high levels of agreement, with consensus ranging from 69.6% to 99.1%.

The high level of agreement could endorse the use of Citomix™ in clinical practice for prevention and early add-on treatment of RRIs. However, it must be underlined that the opinions expressed by these participants reflected their practical experience acquired in daily practice, even though corroborated by the data from preclinical and observational studies.

In conclusion, the results of this Delphi Consensus represented an input for further evidence-based studies highlighting the effectiveness of low-dose medications for both the prevention and treatment of RRIs.

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LECT 5

RATIONAL USE OF NUTRACEUTICALS IN PEDIATRICS

G. Trapani

Alfred Nobel Study Center, Sanremo, Italy

The definition of nutraceuticals (NCs), created in 1989 by Stephen De Felice, is: "A term combining 'nutrition' and 'pharmaceutical' to refer to a food, or part of it, that has a beneficial effect on human health, including the prevention and treatment of disease" [1]. So, have NCs been used for children's health only after 1989? This is false. NCs have been classified into categories such as vitamins and minerals, phytonutrients or phytotherapeutics, essential fatty acids, probiotics and prebiotics, amino acids and peptides, antioxidants, herbs and plant extracts, dietary fibers, bioactive peptides, and functional foods [2]. However, vitamins were discovered between the late 19th and early 20th centuries, and from the 1920s and 1930s, vitamin supplements such as vitamin D for rickets and vitamin C for scurvy began to be produced. Phytonutrients (phytotherapeutics) were already in use around 3000 B.C.E. by the Egyptians and Sumerians (Ebers Papyrus, 1550 B.C.E.) and in China around 3000 B.C.E. (Shennong Ben Cao Jing). Therefore, while the classification is recent, this approach to healthcare is safe and supported by a long-standing history of use. Nevertheless, logic and caution are required when complementing conventional therapies with modern NCs, as inappropriate supplementation can cause side effects or be ineffective. There are conditions that can benefit from the complementary use of these products, such as urinary tract infections, digestive diseases, allergies, recurrent respiratory infections, and metabolic disorders.

In pediatrics, a current challenge is metabolic syndrome (MS), which is often associated with chronic low-grade inflammation, increasing the likelihood of developing cardiovascular diseases and type 2 diabetes in adulthood. Poor diet, excessive consumption of ultraprocessed foods (UPF), and overweight are common problems in both youth and adults. In Italy, childhood obesity is on the rise, with 12.3% of children being obese and 23.6% overweight, increasing the risk of chronic diseases due to adipose tissue-induced inflammation. For the management of MS in pediatric age [3], it is crucial to also consider oral health, often worsened by the consumption of UPF, which contributes to overweight, obesity, and cavities. Probiotics, such as *Streptococcus salivarius M18*, prevent cavities and plaque, improving gingival and dental health, while *Lactobacillus salivarius* reduces harmful bacteria, preventing plaque. Among the NCs useful for maintaining oral health are *Camellia sinensis*; its catechins have antimicrobial and antioxidant effects, helping to fight oral bacteria and prevent cavities. *Cinnamomum verum* (cinnamon) contains eugenol, which reduces the bacteria responsible for plaque and prevents cavities. Cranberry, with its proanthocyanidins A, prevents bacteria from adhering to teeth, reducing the risk of cavities. Vitamin D3 and calcium are essential for enamel mineralization. Lactoferrin, a natural antimicrobial, protects against cavities. Xylitol (as a prebiotic) reduces the growth of cariogenic bacteria. The integration of these elements helps maintain good oral health in children.

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LECT 6

THE PAST, THE PRESENT: WHAT FUTURE FOR PEDIATRICS AND PEDIATRIC SOCIETIES?

S. Vendemmia[1], I. Pezone[2], D. Perri[2], V. Ferrara[3], M. Vendemmia[4]

[1]*Emeritus Chief of Pediatrics and Neonatology, Hospital of Aversa, Aversa, Italy*

[2]*Division of Pediatrics and Neonatology, "San Giuseppe Moscati" Hospital, Aversa, Italy*

[3] General Inspector of Military Health, Rome, Italy
[4]Neonatal Intensive Care Unit, University Federico II Naples, Naples, Italy

The birth of the Italian Society of Hospital Pediatrics (*Società Italiana di Pediatria Ospedaliera* – SIPO) has opened up new avenues for hospital pediatricians who, in spite of less than excellent state support, have always tried, with great difficulty and sacrifice, to provide their care. Hospitalists have often hoped for a better future, for recognition of their efficient and hard daily work, for recognition of their efficiency, merits and preparation by institutions. Hospital physicians, therefore, in order to improve their knowledge and the quality of services provided, have organized numerous congresses and refresher courses in Italy, have "grown up" culturally by comparing and analyzing their heritage of many and countless rare experiences. They have also begun to publish books to publicize the results of their work and experiences.

These initiatives were successful in Italy and, for this reason, the idea of an extraordinary project matured in them, "SIPO in the World". This idea was also born out of the evolution of modern medicine and the awareness of the role that Scientific Societies must assume in national and international relations in the face of new technologies and concepts, the "10 P medicine", from the physician-centric to the patient-centric system, etc. This policy has been very helpful in strengthening scientific, professional and relational collaborative relationships. By now, the Europe of the third millennium cannot only represent a difficult aggregation of peoples and cultures, which are not always similar and concordant, but must also unite the different personalities with mechanisms of collaboration and coordination. These ideas and initiatives, if truly felt, can be another system to facilitate the true aggregation of us Europeans with colleagues from other continents.

SIPO's experience around the world has now exceeded 15 years, achieving extraordinary contributions and successes. On April 20, 2008, in Tehran, SIPO was appointed as a member of the Union of Mediterranean and Middle-Eastern Pediatric Societies (UMEMPS). In December 2008, the first protocol of understanding and collaboration between SIPO and the Turkish Society of Pediatrics was signed in Antalya. Subsequently, Scientific Societies were founded by SIPO members and colleagues from Romania (Italian-Romanian Pediatric Society – IRPS), Arab countries (Italian-Arabic Pediatric Society – IAPS), Albania (Albanian-Italian Pediatric Society – AIPS). We have participated annually in major international events, in Greece, Turkey, Azerbaijan, Romania, Algeria, Cyprus, Georgia, Lebanon, Albania, Jordan, etc. In October 2014, SIPO received an invitation from the American Academy of Pediatrics (AAP) to establish collaborative relationships. SIPO obtained a membership, a board member and a president in the UMEMPS. In addition, during the 8th European Congress of Pediatrics, in Bucharest, four Italians were named Masters of European Pediatrics. Many other colleagues were honored with titles and awards. We have four websites (regarding SIPO, IRPS, IAPS, AIPS, respectively) that are very active.

Finally, "SIPO in the World" has also been thinking about world peace and children victims of wars. That is why it has established an intense collaboration with the Italian Military Health, which operates in dangerous war missions. On March 21, 2024, SIPO and Italian Military Health organized a congress dedicated to world peace in Caserta. For the occasion, Poste Italiane issued three special postcards with a special cancellation. We are waiting for the day of March 21 to be officially recognized as the "World Peace Day Sponsored by Italian Hospital Doctors together with Italian Military Doctors".

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LECT 7

THE FAMILY PEDIATRICIAN AND THE FUTURE

A. D'Avino

Primary Care Pediatrician, Naples, Italy

In Italy, Free-choice Pediatrics operates in respect of the fiduciary relationship with families to meet the principles set forth in Law 833/78, in harmony with internationally codified children's rights. Every resource dedicated to children is not an expense but an investment in the country's future. Free-choice Pediatrics (along with General Medicine) recognizes itself in the conventional contractual form, at the foundations of which are the relationship of trust and the widespread presence, throughout the territory, of our professional practices. These two characteristics bind us to families and characterize a professional figure that is neither negotiable nor replaceable with other forms of care: therefore, the future is already now!

For individuals in the "developmental age" (pediatric-adolescent) the real investment in health is represented by the development of prevention, improvement of lifestyles and support of parenting, obviously alongside the aspects related to both acute and chronic pathology; in addition, today and in the future, we also extend the meaning of prevention to the detection of omissions of care or early interception of forms of child maltreatment or abuse. This is an almost unique responsibility of care in European primary care. Unfortunately, defunding the system and the push for privatization are elements that represent a moment of momentous crisis for public health care. To this must be added the necessary and no longer postponable reform of primary care, which represents the area of our activity and therefore the core of the National Health Service (of the future).

Free-choice Pediatrics is still here, 44 years after its birth, loved and deemed necessary by the population. Today we are even more aware of the needs of families, but in order for the best take-up of care activities to be fully realized, it is necessary that – in the future – more and more attention be paid to investments in the organizational scope of the entire Primary Care sector. Family Pediatricians' practices must be enhanced and implemented with presence of staff, health and non-health adequately trained (nurses and practice associates), equipped with diagnostic equipment (Point of Care Test instruments), so as to be able to best ensure the first level of care and ensure the necessary care governance.

In the future of Primary Care Pediatricians, we will find telemedicine (in all its declinations) and artificial intelligence in order to raise the quality level of services. In order for the National Health Service to be more and more efficient in the coming years, we will need Pediatrics residents to acquire territorial medicine skills. We open the doors of our practices, this is also the future!

LECT 8

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): NEWS AND UPDATES

M. Carotenuto

Child Neuropsychiatry Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Caserta, Italy

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by a persistent pattern of age-inappropriate inattention and hyperactivity-impulsivity, resulting in various degrees of functional or developmental impairment. This leads to cognitive, behavioral, emotional, and social changes that are pervasive in all social settings. The prevalence of ADHD is difficult to establish due to its neurobehavioral nature. However, a prevalence of 5.9% has been found in children and adolescents worldwide, with a persistent prevalence in adults of 2.5%.

ADHD has a high heritability, estimated to range between 70% and 80%, and the GWAS analysis identified 12 loci that contain a DNA variant associated with an increased risk of ADHD. This represents approximately 22% of the heritability of the disorder.

Due to the diverse etiology of ADHD, various risk factors have been associated with the disorder. These are classified into genetic factors, including candidate genes related to ADHD, and environmental factors, encompassing prenatal events involved in the development of ADHD. Genetic studies have shown that ADHD is highly polygenetic, with a genetic architecture explained by thousands of common genetic variants, each with a small effect, as well as rare mutations with a greater effect.

Multiple studies on ADHD-associated candidate genes primarily involve genes related to the catecholaminergic system, including the dopamine transporter gene (*DAT1*), the dopamine D4 receptor gene (*DRD4*), the dopamine D5 receptor gene (*DRD5*), and the catechol-O-methyl transferase gene (*COMT*). Genes related to other neurotransmitter systems, such as the serotonin receptor 1B gene (*HTR1B*) and the nicotinic acetylcholine receptor 4 gene (*CHRNA4*), have also been described. Additionally, genes related to the glutamatergic system, including the ionotropic glutamate receptor and NMDA receptor subunit-encoding genes (*GRIN2A* and *GRIN2B*), as well as genes involved in central nervous system development, such as the *SNAP25* gene, have been associated with ADHD. Genes involved in immune regulation, such as IL-2, IL-6, and TNF-α, have also been reported.

LECT 9

FEVER IN PEDIATRIC PATIENTS: AN EAR-NOSE-THROAT (ENT) PERSPECTIVE

A. Varricchio[1], F.P. Brunese[2], A. Varricchio[3]

[1]Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy
[2]Local Health Authority of Caserta, Caserta, Italy
[3]University Vita-Salute San Raffaele, Milan, Italy

Fever, inflammation, and pain represent a common triad in pediatric care, particularly in oto-rhinolaryngological conditions. Although these symptoms are part of natural defense mechanisms, they often provoke concern and misunderstanding among parents. For example, fever management is frequently associated with an exaggerated perception of risk, a phenomenon known as "fever phobia" [1], which leads to inappropriate interventions aimed at lowering body temperature, thereby neglecting the immunological benefits of fever [2]. Similarly, pain, while serving as a physiological warning signal, is often underestimated, despite its significant impact on the child's overall well-being.

Therapeutic intervention focuses on the judicious and targeted use of antipyretic and anti-inflammatory drugs, particularly paracetamol and ibuprofen, as recommended by Italian guidelines for managing fever and pain in children [3]. These recommendations highlight that paracetamol can be used from birth, while ibuprofen is indicated from the third month of life, both with comparable safety profiles. Of particular interest is the new suspension formulation of ibuprofen lysinate encapsulated in beta-cyclodextrin, which offers more rapid and consistent absorption, along with fewer gastrointestinal side effects, thereby enhancing its efficacy and tolerability.

In the Ear-Nose-Throat (ENT) field, fever and inflammation are closely linked to conditions such as rhinosinusitis, acute otitis media, and pharyngotonsillitis, where the use of non-steroidal anti-inflammatory drugs (NSAIDs) not only modulates fever but also acts on the inflammatory pathogenesis, reducing the duration of the infectious process. Furthermore, a careful differentiation between viral and bacterial infections is recommended to avoid inappropriate antibiotic use, which should be reserved for confirmed bacterial etiologies. Concrete examples include the use of a rapid throat swab for Group A beta-hemolytic *Streptococcus*, crucial for diagnosing bacterial pharyngotonsillitis, and proper otoscopy to reveal tympanic membrane bulging due to purulent effusion, pathognomonic of bacterial acute otitis media.

It is important to emphasize the rhinogenic pathogenesis in viral forms, which benefit from the use of specific aerosol devices, such as micronized nasal douches, that treat the nasal and nasopharyngeal regions, contributing to symptom reduction and the prevention of lower airway complications.

The abstract highlights the importance of a rational and informed therapeutic approach to managing fever, inflammation, and pain in pediatric ENT care, with a focus on educating parents for accurate understanding and management of these symptoms.

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LECT 10

THROMBOCYTOPENIA IN CHILDREN

S. Barella

Thalassemia Unit, Reference Center for Rare Anemias and Iron Metabolism Disorders (in Pediatric and Adult Age) and Non-Oncological Pediatric Hematology, Microcitemico Hospital, Cagliari, Italy

Thrombocytopenia, defined as a platelet count below 150,000/microL, is a common finding in pediatric patients, with presentations ranging from asymptomatic cases to significant bleeding. It can manifest through petechiae, bruising, mucosal bleeding, or more severe complications. In other cases, thrombocytopenia may be incidentally discovered during routine investigations. Immune thrombocytopenia (ITP) is the most frequent cause of isolated thrombocytopenia in children, characterized by platelet counts below 100,000/microL without an underlying disorder.

The risk of bleeding generally correlates with the severity of thrombocytopenia, though this relationship may vary. Children with ITP often have younger, more active platelets, which may reduce bleeding risk despite low counts. Typically, spontaneous bleeding is rare when platelet counts are above 20,000/microL, and surgical bleeding tends to occur with counts below 50,000/microL.

A systematic approach is required for the evaluation of unexplained thrombocytopenia. Laboratory confirmation is crucial to rule out spurious causes

such as errors or platelet clumping. Peripheral blood smear examination provides insights into platelet morphology and other abnormalities. A detailed clinical history is essential to identify potential causes, assess symptom severity, and review factors such as family history, recent infections or vaccinations, medications, and diet.

Management focuses on minimizing bleeding risk, which includes avoiding contact sports or activities that increase the risk of trauma, particularly to the head. Medications that impair platelet function, such as non-steroidal anti-inflammatory drugs (NSAIDs), should be avoided. In cases of severe thrombocytopenia, especially when mucosal bleeding or "wet purpura" is present, close monitoring is necessary due to the higher risk of life-threatening hemorrhage.

Further diagnostic tests may include screening for viral infections, autoimmune disorders, or bone marrow pathology, depending on the clinical picture. Imaging studies and more invasive procedures, such as bone marrow biopsy, may be necessary if malignancy or bone marrow failure is suspected.

In ITP, treatment focuses on managing the bleeding risk rather than normalizing platelet counts. Therapies such as corticosteroids, intravenous immunoglobulin (IVIG), or anti-D immunoglobulin may temporarily increase platelet counts in cases of severe bleeding. For children with chronic or refractory ITP, additional treatments like thrombopoietin receptor agonists may be considered.

Although pediatric thrombocytopenia is often benign, certain patients face a higher risk of severe complications, such as intracranial hemorrhage. This rare but potentially fatal outcome highlights the need for individualized care plans and caregiver education on early signs of bleeding and safety measures. Future research should aim to refine diagnostic criteria for pediatric thrombocytopenia and develop predictive models for identifying children at the highest risk of severe bleeding, while also determining optimal management strategies for thrombocytopenia in different pediatric conditions.

LECT 11

EXPOSURE TO DIGITAL DEVICES IN CHILDHOOD: A STUDY OF 1,332 CHILDREN AND PREADOLESCENTS

L. Pisano[1], O. Al Jamal[2]

[1]*Psychologist and Psychotherapist, Criminology IFOS and Sardinia Cybercrime Observatory, Cagliari, Italy*

[2]*Primary Care Pediatrician, Cagliari, Italy*

The use of digital devices with an internet connection (such as smartphones, tablets, PCs, smart TVs, consoles, smartwatches) is constantly increasing and has become an integral part of our daily lifestyle, indispensable tools for work, school, communication and maintaining relationships. However, children, pre-adolescents and adolescents are increasingly accessing devices at an early age, maintaining excessive levels of screen time and are often exposed to digital content that is not appropriate for their age. Several studies show that the damages resulting from the use of digital devices for the development and behavior of children outweigh the benefits that can be derived from them. The benefits of electronic devices are most often observed only in school settings, with the participation of adults and specific software apps [1].

We have introduced the term "digital health" to indicate a concept of health that interacts with biological, psychological and social health. Digital health indicates, in fact, the well-being or discomfort that all individuals, especially children, pre-adolescents and adolescents, can perceive when they come into contact with digital devices connected to the Internet [2].

To evaluate this aspect of health, the Sardinian Training Institute (*Istituto di Formazione Sardo* – IFOS) in collaboration with the Italian Federation of Pediatric Doctors (*Federazione Italiana Medici Pediatri* – FIMP), in 2021, designed a specific computerized procedure, the "Evaluation of Digital Health" (EDH), which allows us to evaluate the adequacy of the electronic tools used, the exposure times and whether the digital contents viewed are compatible with the age and psycho-physical characteristics of the child; the possible consequences on the psycho-physical and social health status are also detected.

We are currently conducting studies in several cities in different Italian regions: the studies are conducted by family pediatricians using the EDH software. The research to which this abstract refers was conducted between July 2022 and August 2023 in primary and secondary schools in the Sardinian territory that joined the initiative. An online questionnaire was used to collect data aimed at knowing the digital health status of children and pre-adolescents. The questionnaire was administered anonymously fol-

lowing the signing of the informed consent of the students' parents.

A total of 1,332 students participated in the study, divided into two age groups:

- 457 children between 9 and 10 years old, of which 226 males (49.45%) and 231 females (50.55%);
- 875 pre-adolescents between 11 and 13 years old, of which 447 male (51.08%) and 428 female (48.92%).

The analysis of the data reveals that the digital health of children and pre-adolescents is at high risk.

The results indicate that 84.83% of the subjects received a smartphone as a gift between the ages of 5 and 10. The daily usage time of devices – specifically smartphones and tablets – was found to be a medium-high risk situation; a high percentage of subjects can keep their mobile devices during the night. We also investigated the supervision of parents' digital activity through parental control applications or other tools. The results show that children and pre-adolescents are not adequately supervised by their parents. In addition to digital habits, the questionnaire also investigates the use of messaging apps and social networks. The survey shows that 88.86% of children, who have a smartphone, use WhatsApp. An alarming percentage of children, 63.96%, has a personal profile on one or more social networks – specifically Instagram, TikTok, Snapchat and BeReal – or uses their parents' profile. The percentages tend to increase further in pre-adolescents. In fact, 97.76% of children between the ages of 11 and 12 use WhatsApp and 83.68% use social networks including TikTok, BeReal, Snapchat, Instagram and NGL.

Finally, in the survey on the exposure of children and pre-adolescents to digital content that is not appropriate for their age, the responses revealed a situation of significant risk.

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LECT 12

PRESENTATION OF THE BOOK "*PEDIATRIC ELECTROCARDIOGRAPHY – A SIMPLIFIED APPROACH*"

F. De Luca

Former Director of Pediatric Cardiology, AUO Vittorio Emanuele, Catania, Italy

The book "*Pediatric Electrocardiography – A Simplified Approach*" is intended as an innovative work, aimed primarily at neonatologists and pediatricians, but also at cardiologists, family pediatricians, ambulance, sports and emergency room physicians. The result of years of experience in the field and conducting more than 120 electrocardiography (ECG) courses, the text offers a comprehensive guide for anyone wishing to learn more about or approach the discipline of pediatric ECG for the first time.

The author has placed great emphasis on creating a book that is usable for both experienced professionals and novices approaching this fascinating branch of medicine for the first time. The structure of the volume has been carefully designed to ensure a balance between theory and practice, with simple, accessible language that makes reading a stimulating and engaging experience.

One of the distinctive aspects of the text is its rich graphic component. Iconographies and illustrations have been strategically placed to facilitate understanding of complex concepts, making learning intuitive and immediate. Each chapter concludes with sections called "*In-Depth Focuses*" and "*Key Points*", which allow the reader to fixate on key concepts and stay up-to-date on industry news. This combination of expository clarity and continuous updating makes the book an essential tool for professional training.

In addition to theory, the book offers a particularly rich and interactive practical section. In it, the reader is guided through clinical cases, multiple-choice quizzes, and electrocardiograms taken from real-life situations, allowing the reader to put the knowledge gained into practice. Open ECGs are presented, which the reader is invited to describe using a reporting template, with solutions available in a digital supplement. This interactivity helps consolidate skills in the diagnosis and management of children's heart disease.

The digital version of the book is an additional tool available to the reader. In it, the author has included a collection of more than one hundred scientific articles, selected from the most relevant in the international publication landscape, accessible via the QR code at the end of each chapter. These

resources allow readers to delve deeper into the topics covered and explore areas of greatest interest with scientific rigor and constant updating. An additional strength of the text is its ability to translate technical concepts into simple, clear language without compromising its scientific rigor. Each chapter is accompanied by summaries of key points, designed to facilitate the assimilation of information and ensure a solid understanding of the basics of the discipline.

The clear structure, engaging graphics, continuous updating, and balance between theory and practice make "*Pediatric Electrocardiography – A Simplified Approach*" a landmark text in the pediatric cardiology medical education landscape. It aims to revolutionize the diagnostic and management approach to cardiac disease in the youngest children, making even the most complex aspects accessible and understandable.

Following are brief excerpts from the introductions to the volume:

- "*The work is absolutely valid... The content is comprehensive, exhaustive, but at the same time easy to understand... At the end of each chapter the reader can't wait to start the next one, as if it were a novel that thrills him more and more as he continues reading it...*" – Mario Carminati;
- "*...I can undoubtedly say that the world of pediatrics finds a new editorial benchmark with the arrival of 'Pediatric Electrocardiography – A Simplified Approach'... The author's undisputed expertise, commitment and masterful attention shines through from every page...*" – Francesco Chiarelli;
- "*...Each page demonstrates experience and passion, those of a lifetime dedicated to children with heart disease... Each page, one senses, has been written with such care and precision as to make this volume an indispensable reference for the subject...*" – Vassilios Fanos.

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LECT 13

PRESENTATION OF THE BOOK "*NUTRACEUTICALS IN CLINICAL PRACTICE: SUPPLEMENTATION AND PREVENTION, A REASONED APPROACH TO HEALTH AND WELLNESS*"

G. Trapani

Alfred Nobel Study Center, Sanremo, Italy

Nutraceuticals play a significant role in safeguarding the health of both children and adults. Given the increasing industrial interest and their importance in disease management, a work that dispels myths and false hopes while promoting an evidence-based approach rooted in scientific and clinical knowledge is essential. The book "*Nutraceuticals in Clinical Practice: supplementation and prevention, a reasoned approach to health and wellness*" [1] provides such information and emphasizes the importance of skepticism in medicine, encouraging doctors not to take anything for granted but to rely on studies and research, their clinical experience, and their understanding of patients.

The nutraceutical approach can significantly contribute to the personalization of therapies. Physicians must apply a comprehensive approach, combining nutraceuticals with lifestyle modifications and, when necessary, pharmacological therapies. This process requires continuous updating of medical knowledge and a deep understanding of the context in which the patient lives. Nutraceuticals do not offer miraculous solutions, but they can be a valuable support for improving patient health. Only through an integrated and personalized approach can significant and lasting results be achieved.

The book "*Nutraceuticals in Clinical Practice: supplementation and prevention, a reasoned approach to health and wellness*" [1] targets doctors, pediatricians, and enthusiasts of the subject, providing clarity in a field often confused with dietary supplements, functional foods, novel foods, and herbal medicines. The lack of approved therapeutic indications further complicates the situation, making a clear and detailed guide necessary. It is essential to distinguish between different products and understand their potential and limitations.

The structure of the book is divided into three parts: the first offers general definitions of various active principles; the second presents quick reference sheets on commercially available nutraceuticals; the third focuses on clinical practice, both as a preventive measure and as support in various clinical conditions. Each section is designed to provide useful and practical tools for health professionals, allowing them to best integrate nutraceuticals into their daily practice.

Numerous studies have demonstrated the efficacy of nutraceuticals in treating various clinical disorders. Calcium, vitamin D, folic acid, and resveratrol have been highlighted for their role in reducing blood pressure and preventing hypertensive disorders during pregnancy [2]. Supplementation with curcumin, psyllium, and *Nigella sativa* has shown positive effects on weight loss in overweight or obese adults [3]. Attention deficit hyperactivity disorder (ADHD), a neurodevelopmental disorder, has a better prognosis with a healthy diet such Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets, and nutritional supplements such as vitamin D, magnesium, zinc, and iron have potential benefits in managing ADHD symptoms [4].

The goal is to provide users with a clear and practical understanding of nutraceuticals, not as definitive solutions, but as components of an integrated approach to wellness and health to improve patients' quality of life and offer personalized solutions based on scientific evidence.

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LECT 14

PRIMARY HYPEROXALURIA TYPE 1

V. Manca, G. Masnata

Department of Pediatrics, Complex Diseases and Pediatric Nephrourology, Brotzu Hospital, Cagliari, Italy

Primary hyperoxaluria type 1 (PH1) is a rare genetic disorder characterized by the overproduction of endogenous oxalate. It is a contributing factor in 1-2% of cases of end-stage renal disease (ESRD) in childhood.

The prevalence of PH1 is estimated to be between 1-3 cases/1 million population, with an incidence of 1 case in 120,000 births in Europe.

The condition is transmitted autosomal recessively, with more than 200 mutations affecting the *AGXT* gene (chr 2q37.3) having been identified. PH1 is caused by a deficiency of the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which catalyzes the conversion of glyoxylate to glycine. A reduction or absence of AGT activity results in the conversion of glyoxylate to oxalate, which cannot be metabolized and must be excreted by the kidneys.

This leads to the formation of kidney stones, nephrocalcinosis, and ESRD. Impaired renal function causes an increase in plasma oxalate levels, leading to the development of systemic oxalate deposition, multi-organ failure and death. The onset of disease ranges from childhood to the 6th decade of life, but most symptoms appear in the first 10 years of life. The clinical manifestations are heterogeneous, some patients present severe symptoms, including failure to thrive and neonatal ESRD.

When plasma oxalate reaches saturation values, calcium-oxalate crystals are formed and deposited in various tissues, including bones, skin, retina, nerves and heart, which can lead to serious diseases.

The primary diagnostic test is the measurement of the 24h urinary oxalate, or oxalate/creatinine ratio in spot urine in toddlers. If hyperoxaluria is present, PH1 genetic testing is strongly recommended. Furthermore, it is useful to measure the other urinary metabolites (glycolate, L-glycerate, 4-OH-2-oxoglutarate, 4-OH-glutamate).

Early diagnosis and treatment are essential to prevent kidney damage and to avoid the disease progression.

The goals of conservative treatment are to prevent urinary calcium-oxalate supersaturation and to reduce the formation of kidney stones. The initial treatment, vitamin B6 supplementation, can lead to a reduction in the excretion of calcium-oxalate in approximately 30% of patients. Conservative measures such as a high fluid intake and potassium citrate administration are indicated, particularly in children, to prevent renal failure and the formation of new kidney stones. The care of pediatric PH1 patients can present significant challenges, and the use of a gastrostomy or nasogastric tube may be required. For many years, the only available option for rectifying glyoxylate metabolism was liver and kidney transplantation (either simultaneous or sequential) in cases of renal failure.

The advent of RNA interference drugs could dramatically improve the outcome of these children, by reducing urinary and plasma oxalate levels.

Further studies are required to evaluate the long-term safety of these drugs and their capacity to prevent systemic hyperoxalosis, thereby replacing liver transplantation, which has hitherto been the sole specific therapeutic option.

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LECT 15

HEREDITARY HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH)

S. Muntoni, C. Piras, L. Atzori

Department of Biomedical Sciences, University School of Cagliari, Cagliari, Italy

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic biallelic disorder with a prevalence of 1 in 250,000 to 360,000. This syndrome is characterized by high levels of plasma cholesterol from birth, rapidly progressive atherosclerotic cardiovascular disease, premature mortality. In Italy, the presence of approximately 200-250 HoFH patients is estimated. Pathogenic variants in genes associated with low-density lipoprotein receptor (LDLR) function result in severely increased LDL-cholesterol (LDL-C) levels. Variants in three of the causal genes – *LDLR* (90%), *APOB* (8%), and *PCSK9* (1%) – display autosomal semidominant inheritance, while variants in the *LDLRAP1* gene (1%) underlie a rare recessive form of HoFH.

European Atherosclerosis Society (EAS) Criteria for the diagnosis of HoFH: genetic confirmation of two mutated alleles at the loci for *LDLR*, *APOB*, *PCSK9* or *LDLRAP1*. Alternatively (clinic); untreated LDL-C > 13 mmol/L (500 mg/dL) or treated > 8 mmol/L (300 mg/dL) together with cutaneous or tendon xanthomas before the age of 10; untreated LDL-C levels consistent with HoFH in both parents. The cumulative LDL-C burden is substantial from birth onwards, giving rise to a very high risk of premature atherosclerotic cardiovascular disease (ASCVD). HoFH patients with markedly elevated LDL-C levels develop early onset cardiovascular diseases such as coronary artery disease, myocardial infarction, severe aortic stenosis, heart failure, stroke, sudden death, symptoms such as tendonitis or arthralgia, skin/tissue lesions such as xanthomas, xanthelasmas, corneal arch. Patients with HoFH may already experience an ASCVD event before reaching adulthood or before the condition is diagnosed and treatment can be initiated.

HoFH therapeutic targets according to EAS recommended treatment goals for LDL-C lowering therapy: adults with cardiovascular complications LDL-C < 1.4 mmol/L (< 55 mg/dL); adults without cardiovascular complications LDL-C < 1.8 mmol/L (< 70 mg/dL); children LDL-C < 3.5 mmol/L (< 135 mg/dL).

Treatment generally consists of a combination of lipid-lowering therapies, such as statins and ezetimibe, but also lipoprotein apheresis, and novel treatment strategies, such as proprotein convertase subtilisin/kexin type 9 inhibition, microsomal triglyceride transfer protein inhibition (lomitapide), bempedoic acid or angiopoietin-like 3 (ANGPTL3) blockade (evinacumab). Prevention is crucial considering that a 1% drop in cholesterol levels leads to a 3% drop in cardiovascular risk for prolonged exposure.

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LECT 16

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

A. Pietrobattista

UOC Metabolic Diseases and Hepatology, UOS Liver Transplantation Clinic Bambino Gesù Children Hospital, IRCCS, Rome, Italy

INTRODUCTION

Infantile cholestasis encompasses a diverse group of disorders characterized by impaired bile flow. Among the intrahepatic causes, progressive familial intrahepatic cholestasis (PFIC) represents a genetically heterogeneous group of autosomal recessive liver disorders. PFIC pathophysiological hallmark is a defective bile secretion and transport across the hepatocellular canalicular membrane, leading to chronic cholestasis, liver fibrosis, and, ultimately, cirrhosis [1]. Early diagnosis is crucial to prevent long-term complications and improving clinical outcomes. PFIC is subdivided into several distinct subtypes based on the specific gene involved. The most well-characterized forms include:

- PFIC1: this subtype involves variants in the *ATP8B1* gene, which encodes the FIC1 protein, involved in maintaining bile salt homeostasis;
- PFIC2: mutations in the *ABCB11* gene, which encodes the bile salt export pump (BSEP). Loss of BSEP function leads to severe cholestasis due to impaired bile acids (BA) efflux;
- PFIC3: this subtype results from variants in the *ABCB4* gene, which encodes multidrug resistance protein 3 (MDR3), a phosphatidylcholine flippase essential for the secretion of phospholipids into bile.

Recent advances in genetics identified new forms of PFIC in addition to the well-characterized PFIC1, PFIC2, and PFIC3 subtypes expanding the spectrum of the disease, among others:

- PFIC4, caused by variants in the *TJP2* gene and PFIC5 in the *NR1H4* gene.

DIAGNOSIS

Diagnosis of PFIC is established through a combination of clinical, biochemical, and histological findings, supported by genetic testing to identify disease causative pathogenic variants. Serum BA levels are typically elevated, while gamma-glutamyl transferase levels remain low but are elevated in PFIC3, reflecting the different pathophysiology between the subtypes. Liver biopsy is not always mandatory when molecular diagnosis is available. As genetic testing becomes more accessible, the identification of newer PFIC variants is expected to improve in the next years [1, 2].

TREATMENT

Historically, medical treatment in PFIC was unsatisfactory and limited to:

- enhancing the bile flow and inhibiting the accumulation of metabolites in the liver (UDCA);
- treatment of pruritus, a major debilitating symptom;
- supporting nutrition to avoid fat and fat-soluble vitamins malabsorption, thus preventing malnutrition.

An emerging therapeutic medical approach in the management of PFIC involves the use of BA reabsorption inhibitors. This new group of drugs specifically targeting the enterohepatic circulation aims to reduce the total BA pool, which is a key driver of cholestatic itch and liver damage [3].

Following failure of medical treatment, liver transplantation is usually required.

CONCLUSION

Advances in genetic research have broadened our understanding of PFIC, with newly identified subtypes and targeted therapies providing hope for more effective treatments.

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LECT 17

ALFA MANNOSIDOSIS: A CHALLENGING DIAGNOSIS FOR A TREATABLE DISEASE

M. Balzarini[1], F. Zanco[2], C. Sbaffi[2]

[1]Complex Diseases and Pediatric Nephrourology Unit, ARNAS Brotzu, Cagliari, Italy
[2]School of Pediatrics, University of Cagliari, Cagliari, Italy

Alpha-mannosidosis (AM) is a rare, autosomal recessive storage disorder caused by deficiency or absence of lysosomal enzyme alpha (α)-mannosidase, resulting in progressive accumulation of mannose-rich oligosaccharides in various tissues and consequent impairment of cell function and apoptosis [1, 2].
The clinical presentation is multisystemic and heterogeneous, ranging from recurrent infections, hearing impairment, hypotonia, language delay and macrocephaly with coarsening facial features to cognitive impairment, gibbus and dysostosis multiplex, ataxia and psychiatric symptoms [1, 2]. Three phenotypic subtypes have been described: a mild and a moderate form, in a clinical continuum, and a severe form with early childhood onset [2].
Diagnosis is often challenging due to the non-specificity of signs and symptoms [3]. The raise of clinical suspicion must lead to biochemical tests or enzymatic dosage, before or in the meantime of genetic testing. In particular, urinary oligosaccharides determination can show specific patterns, allowing a relatively rapid and inexpensive diagnosis, or orienting next generation sequencing (NGS) testing.
Until a few years ago, the only available therapy was hematopoietic stem cells transplantation, to be performed in the first decade of life [2]. In 2018 enzyme therapy with velmanase alfa (VA) was approved in Europe. It is a recombinant human product which supplements endogenous α-mannosidase, reducing serum levels of oligosaccharides, increasing immunoglobulin G levels, and improving the functional capacity and quality of life of patients [2, 3]. The effects are greater in early treatment, before extensive and irreversible oligosaccharides tissue accumulation [2]. Long-term VA treatment outcomes are still being elucidated, targeting only non-central nervous system involvement.
Aside therapy, multidisciplinary and supportive care are the gold standards for management, to improve patients' quality of life, maximize function and reduce complications. Patient should be monitored on supportive care every 6 to 12 months [1].
To conclude, increasing clinical awareness of AM can reduce the diagnostic delay, and biochemical and enzymatic testing, together with genetic NGS testing, should be performed to assess or orient the genetic diagnosis, allowing patients to access the benefits of early and timely treatment and careful management by specialists [2].

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LECT 18

LYSOSOMAL ACID LIPASE (LAL) DEFICIENCY: CLINICAL SPECTRUM, DIFFERENTIAL DIAGNOSIS AND SPECIFIC THERAPY

V. Casotti

Hepatology, Gastroenterology and Liver Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, Italy

Lysosomal acid lipase (LAL) deficiency (LAL-D) is an ultra-rare, autosomal recessive disease, firstly described by Wolman in 1956, belonging to the group of lysosomal storage diseases, due to a defect in lysosomal proteins or enzymes. In this condition, the lacking protein is LAL, involved in degradation of cholesteryl esters and triglycerides, localized on chromosome 10 (10q23.2); the most common mutation on *LIPA* gene is a splice junction on exon 8 (E8SJM – c. 894G>A). The absence or reduced activity of the protein leads to accumulation of triglycerides and cholesteryl esters in cell lysosomes of different tissues, with subsequent multi-organ involvement (liver, hearth, bowel and spleen).
The prevalence ranges from 1:40,000 to 1:300,000, and there is a wide spectrum of clinical presentations, both in terms of severity and age at onset. We can distinguish:

- Wolman disease (early onset LAL-D): the LAL enzyme activity is almost completely absent, the disease starts in the neonatal period and has a severe course, characterized by vomiting, diarrhea, failure to thrive, hepatosplenomegaly, cholestasis, adrenal gland calcifications; without

any treatment, the life expectancy is less than 12 months;
- cholesteryl ester storage disease (CESD, late onset LAL-D): the LAL enzyme activity is until 10%, the disease onset can be from childhood to adulthood, and the course is slowly progressive, characterized by dyslipidemia, hypertransaminasemia, hepatomegaly +/- splenomegaly, progressive liver disease and early atherosclerosis.

Even though this is a rare disease, it is mandatory to consider it in the differential diagnosis with other groups of conditions, presenting with some common characteristics. In particular: other lysosomal storage diseases with liver involvement (Gaucher, Niemann Pick type B or C), other cirrhotic liver diseases (autoimmune hepatitis, cryptogenic cirrhosis), other metabolic or genetic liver diseases (Wilson disease, alfa1-AT deficiency), the familial hypercholesterolemia, the NAFLD/NASH and MAFLD.

The right diagnosis of LAL-D allows the possibility of a specific treatment: since 2015, the natural history of this disease has changed, due to the availability of an enzyme replacement therapy, with sebelipase-alfa. The periodical enzyme infusion in affected patients leads to significant improvement in liver and lipid profile, possibly life saving for Wolman disease, and preventing the progression to liver fibrosis and cirrhosis in CESD.

The rarity of the disease and the advancements in the treatment gave the impulse to the creation of an International Registry, started in 2013, to collect longitudinal data about patients. The aim of the registry is to evaluate the natural history of the disease, the long-term course and complications, the efficacy and safety of sebelipase-alfa and other treatments, the "real life" management of patients. To date, more than 250 subjects are included, coming from 103 Centers, in 23 countries.

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LECT 19

AROMATIC L-AMINO ACID DECARBOXYLASE (AADC) DEFICIENCY

T. Foiadelli

Pediatric Clinic, University of Pavia, Pavia, Italy

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, autosomal recessive neurometabolic disorder caused by mutations in the *DDC* gene, leading to impaired synthesis of dopamine, serotonin, and other catecholamines. Epidemiologically, AADC deficiency is an ultra-rare condition with a global prevalence that remains largely underreported, likely due to challenges in diagnosis.

Clinically, patients with AADC deficiency typically present in infancy or early childhood with severe hypotonia, oculogyric crises, developmental delays, and autonomic dysfunction. The phenotypic spectrum is broad, ranging from mild to severe forms, complicating clinical recognition.

Diagnosis relies on a combination of clinical features, biochemical analysis showing reduced levels of cerebrospinal fluid neurotransmitters, and confirmatory genetic testing. Early diagnosis is crucial, as untreated AADC deficiency can lead to significant morbidity and mortality.

Therapeutically, management includes a combination of pharmacological interventions aimed at enhancing residual enzyme activity, providing dopamine receptor agonists, and addressing associated symptoms. Recent advances have also introduced gene therapy as a promising treatment, highlighting the potential for improved outcomes.

Given the availability of treatment options, the importance of early diagnosis cannot be overstated. Increased awareness among clinicians, along with advances in diagnostic techniques, could lead to earlier detection and intervention, thereby improving the quality of life and prognosis for affected individuals.

LECT 20

ROLE OF ALKALINE PHOSPHATASE IN THE DIAGNOSIS OF HYPOPHOSHATASIA

S. Savasta

Pediatric Clinic and Rare Diseases, "Microcitemico Hospital", University of Cagliari, Cagliari, Italy

Alkaline phosphatase (ALP) is an enzyme present mainly in bones, liver and kidneys. It plays an important role in bone mineralization and its deficiency compromises bone growth. ALP is also responsible for hydrolysis of pyridoxal-5-phosphate, the active form of vitamin B6, to pyridoxal. Low ALP activity is considered biochemical marker of hypophosphatasia (HPP), a rare inherited metabolic disease caused by mutation in the *TNSALP* gene. This pathology can be inherited in autosomal recessive or dominant mode, and the latter form is associated with mild phenotypes. Low levels of ALP can also be present in conditions other than HHP: pregnancy, drug administration (glucocorticoids, estrogens, bisphosphonates), hypothyroidysm, celiac disease, anemia and malnutrition. Due to these conditions and the onset of mild symptoms, the disease is often underdiagnosed. The symptoms at onset are varied with a spectrum of severity and based on the age of onset. Four main forms of HHP are considered (perinatal, infantile, juvenile, adult). The phenotype is different in the forms of HHP and symptoms such epilepsy are characteristic when the onset occurs in the first months of life. Although the most severe forms are those with early onset, the mild forms diagnosed in adulthood are associated with severe and debilitating complications. Therefore, early detection of the disease is important for both severe and mild forms, in which a specific therapy can now modify the clinical course. A novel enzymatic therapy for HHP, asfotase alfa, is now available.

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LECT 21

DONKEY MILK BETWEEN PAST AND FUTURE

V. Fanos[1,2], M. Corridori[3]

[1]*Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy*

[2]*Department of Surgical Sciences, University of Cagliari, Cagliari, Italy*

[3]*Hygeia Press, Quartu Sant'Elena, Italy*

Donkey milk has a long history, valued for its medicinal and cosmetic properties as far back as ancient times. In ancient times, it was highly sought after for its properties similar to human breast milk. Doctors such as Hippocrates and Galen recommended it to treat gastrointestinal and respiratory disorders and as baby food. Cleopatra and Poppaea Sabina, wife of Nero, used it in baths to preserve the beauty of the skin. Donkey milk was considered an elixir of health and beauty among the noble and medical classes of the time.

In the Middle Ages, donkey's milk continued to be used, especially in folk medicine, to treat ailments such as tuberculosis and digestive problems, although its application was more limited than in antiquity because of superstition-related fears. With the Renaissance and the rediscovery of classical texts, donkey milk came back into vogue, especially for infant nutrition and for its healing properties against respiratory diseases. In the Modern Age (17^{th}-19^{th} centuries), donkey milk found a new impetus. It was used in hospitals and sanatoriums for infants and patients convalescing or suffering from tuberculosis. Its cosmetic use grew considerably, with the noble classes considering it a beauty secret for the skin.

Today, donkey milk continues to be prized for its breast milk-like properties, with a low fat content and a composition rich in vitamins and minerals. It is particularly suitable for people allergic to cow's milk, those with digestive disorders, and those seeking a healthy, light diet. Its immune-stimulating and antioxidant properties make it useful for strengthening the immune system and fighting inflammation.

In the modern cosmetics industry, donkey milk is used in creams, soaps and anti-aging products because of its moisturizing, regenerative and anti-inflammatory properties. However, production is limited due to the low yield of donkeys (about 1-2 liters of milk per day), which makes the product expensive. Countries such as Italy, France and Turkey are the main producers, with a growing demand for donkey milk in both food and cosmetics.

Modern scientific research continues to explore the potential of donkey milk, particularly in the field of functional foods and dermatological treatments. Its antioxidant and antitumor properties are the subject of ongoing studies, solidifying its reputation as a natural and health product for both medicine and beauty.

In the pediatric field, recent groundbreaking work involving the application of metabolomics to the

study of donkey milk fortificants for the milk of mothers of preterm infants should be mentioned.

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LECT 22

THE QUALITY OF DONKEY MILK

M. Martini

Department of Veterinary Sciences, University of Pisa and Interdepartmental Research Center Nutrafood "Nutraceuticals and Food for Health", Pisa, Italy

The milk composition of all mammals is species-specific for the development of offspring. Almost all commercial milk comes from ruminants, whereas donkey milk is produced by a monogastric (like the human being). Over the last 15 years, studies on the quality of donkey milk have increased exponentially and research has shown that the composition of donkey milk is more similar to human milk than polygastric milk. In particular, the average total protein content (1.6 g/100 ml) and protein profile of donkey milk are closer to human milk. The lower total casein content (0.7 g/100 ml), mainly the lower alphaS1 and alphaS2 content, which are especially allergenic, favor its tolerability in 83-98% of those children that are allergic to the proteins in cow's milk [1]. In addition, as in human milk, the higher content of total whey proteins (0.6 g/100 ml) compared to ruminant milk, together with the greater degradability of the protein fractions, favor a more friable and more easily digestible clot [2]. The high lysozyme content (0.15 g/100 ml) contributes to the antibacterial activity of donkey milk. The high degree of similarity in the amino acid profile with human milk and in particular in the essential amino acid content is particularly important for infant nutrition. The lactose content of donkey milk is similar to human milk (on average 6.5-7 g/100 ml) which is important since lactose is a prebiotic and favors the palatability of donkey milk, thus making the taste of milk acceptable for children. The average content of minerals (0.36 g/100 ml) is closer to human milk and about a half that in ruminant milk. The low intake of minerals and total proteins reduces the renal load. Donkey milk also has a relatively high content of vitamin D (vitamin D2 1.64 and D3 0.60 µg/100 ml). The lower fat content (0.3-1.4 g/100 ml), compared to human milk, reduces donkey milk energy to about 410 Kcal/L. Donkey milk, therefore, requires adequate daily energy supplementation based on the age of the children, such as extra virgin olive oil and glucolipid supplements in infants [3]. Compared to ruminant milk, the fatty acid composition is of nutritional interest due to the reduced percentage of saturated fatty acids and the higher content of unsaturated fatty acids (about 50% of the total fatty acid content), especially alpha-linolenic acid (8 g/100 g of fat), precursor of omega 3, and EPA (0.35 g/100 g of fat). The fat globules have an average diameter of 1.92 microns, which is smaller than that reported for ruminant milk, thus contributing to its digestibility.

In conclusion, donkey milk has more similarities with human milk than the milk of any other livestock species. It can be considered milk with low allergenic potential, is more digestible, and has a low impact on the renal load.

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LECT 23

DONKEY MILK: A RESOURCE IN PRETERM INFANTS NUTRITION

E. Bertino[1], G. Maiocco[1], L. Cavallarin[2], M. Giribaldi[2], S. Deantoni[1], C. Peila[1], A. Coscia[1]

[1]Neonatal Unit of the University of Turin, Turin, Italy

[2]Institute of Sciences of Food Production, National Research Council, Grugliasco, Italy

Benefic proprieties of donkey milk are known since ancient times, but in the last decades the scientific community has carried out in-depth studies on the value of this milk in human nutrition, emphasizing its great similarity with human milk (HM) in terms of macro- and micronutrients composition. Bearing

this in mind, it is possible to consider that donkey milk could be suitable to produce an HM fortifier useful in feeding preterm infants during their Neonatal Intensive Care Units (NICUs) stay. Our research group has therefore created a novel donkey milk-derived fortifier (DMF), and randomized controlled trials have been made to compare DMF with the classic bovine milk-derived fortifier (BMF). Results of the studies demonstrated that DMF could improve feeding tolerance and reduce gastroesophageal reflux episodes in preterm infants compared to BMF, with similar auxological outcomes when infants have been discharged from NICUs [1, 2].

Regarding digestomics, a study was conduct to determine if enriching HM with either the DMF, containing whole donkey milk proteins, or a commercial BMF, containing hydrolyzed bovine milk whey proteins, affects the release of peptides during digestion. Results indicated that the different fortifiers did not significantly alter the overall intensity of HM peptides; however, fortification led to distinct impacts on the release of specific bioactive peptides, with DMF-digestion generating extra anti-inflammatory peptides. Additionally, when HM was supplemented with DMF, there was a minor delay in the release of peptides from lactoferrin and beta-lactalbumin. This prolonged presence of intact lactoferrin holds promise for bolstering gut protection against infections and inflammation.

Long-term follow-up data suggest that DMF does not impact the development of allergic manifestations in the first 6-8 years of age [3]. Finally, two studies demonstrated no differences between DMF and BMF regarding auxological and neurodevelopmental outcomes at 24 months of age. Rising scientific knowledge in donkey milk properties allow us to state, in agreement with a previous *Telegraph* article, that donkey milk could be "the next big thing" in neonatal nutrition.

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LECT 24

METABOLOMICS OF DONKEY MILK

F. Cesare Marincola[1], V. Fanos[2,3]

[1]Department of Geological and Chemical Sciences, University of Cagliari, Cagliari, Italy

[2]Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy

[3]Department of Surgical Sciences, University of Cagliari, Cagliari, Italy

Metabolomics, the comprehensive study of low molecular weight (< 1.5 kDa) metabolites in biological systems, has emerged as a powerful tool for analyzing milk composition [1]. Milk, a complex and dynamic fluid, provides essential nutrients and bioactive compounds crucial for neonatal growth and development. The application of metabolomics to milk offers deep insights into its biochemical complexity and variability, influenced by factors such as lactation stage, diet, genetics, and environmental conditions. Techniques such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) have been employed to profile a wide array of metabolites in milk. These technologies enable the identification and quantification of small molecules like amino acids, carbohydrates, lipids, vitamins, and nucleotides. This comprehensive understanding of milk composition has significant implications for health and nutrition. Beyond these aspects, milk metabolomics can contribute to personalized nutrition by tailoring dietary recommendations based on individual metabolic profiles. This approach could optimize maternal and infant health outcomes by ensuring that specific nutritional needs are met through targeted dietary interventions.

Additionally, metabolomics has been employed to study milk formulas derived from various animal sources, including bovine, caprine, and, more recently, donkey milk. Each type of milk has a distinct metabolic profile that impacts its nutritional and health benefits. Metabolomics studies have highlighted the unique compositions of these milk types, providing insights into their suitability for different dietary needs. Understanding these differences can guide the development of tailored milk formulas to meet the diverse nutritional requirements of infants. This application of metabolomics is particularly valuable, as it allows

for the creation of specialized formulas that can better match the nutritional needs of infants who may not be able to consume human milk, thereby enhancing their growth and development.

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LECT 25

THE VIRTUAL KIDNAPPING OF YOUTH BY SOCIAL MEDIA

M. Leiner

Department of Pediatrics, Texas Tech University Health Sciences Center, El Paso, Texas, USA

The pervasive influence of social media has transformed the landscape of media consumption among youth, ushering in a new era of virtual connectivity and engagement. This shift has not been without consequences, as adolescents find themselves consistently engaged in a digital realm where the boundaries between reality and virtuality are blurred. The phenomenon of "virtual kidnapping" by social media platforms is a stark reality, where young individuals are lured into a world of constant connectivity and engagement, often at the expense of their well-being.

Central to this virtual kidnapping is the success of advertising practices on social media platforms. Marketers have harnessed the power of personalized advertising, leveraging algorithms to tailor content to individual users' interests and behaviors. The 24/7 availability of online content ensures that adolescents are constantly bombarded with marketing messages, creating a digital environment where consumerism thrives, and personal well-being is set aside [1].

Furthermore, the manipulation of algorithms as noted by scholars like Safiya Umoja Noble [2], sheds light on how search engines and social media platforms perpetuate existing social inequalities, particularly concerning race and gender. These algorithms reinforce systemic biases and discriminatory practices, shaping public perceptions and reinforcing stereotypes about marginalized communities. This manipulation can have profound implications for young individuals, influencing their beliefs, and future leadership.

Within this ongoing system of media engagement, adolescents find themselves grappling with a myriad of mental health challenges. Rates of depression, anxiety, and suicide among young people are on the rise, with social media exacerbating feelings of inadequacy, loneliness, and fear of missing out. The constant connectivity and comparison fostered by platforms like Instagram and Snapchat have created a culture of self-doubt and low self-esteem, leaving adolescents vulnerable to psychosocial and behavioral problems [3].

The concept of "phone-based childhood" encapsulates the harm wrought by excessive social media use, leading to social deprivation, sleep disruption, attention fragmentation, and addiction among young users. The addictive features of social media platforms, such as notifications and likes, tap into the brain's reward system, fostering a cycle of compulsive use and potential addiction. Children and adolescents, in particular, are susceptible to these manipulative practices, often unaware of the detrimental impact on their well-being.

In conclusion, the virtual kidnapping of youth by social media, fueled by the advertising success of all times, poses a significant threat to adolescent well-being. As young individuals navigate the digital landscape, it is imperative to raise awareness about the risks associated with excessive media consumption and the insidious nature of targeted advertising on social media platforms.

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