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Lectures

Selected Lectures of the Meeting "Rare diseases: diagnostic pathways and new therapies", including the session on the Life MILCH project and the session titled "They will be famous"

CAGLIARI (ITALY) · OCTOBER 18TH, 2023

The Meeting "Rare diseases: diagnostic pathways and new therapies", including the session on the Life MILCH project and the session titled "They will be famous", is a Satellite Meeting of the 19th International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 18th-21st, 2023.

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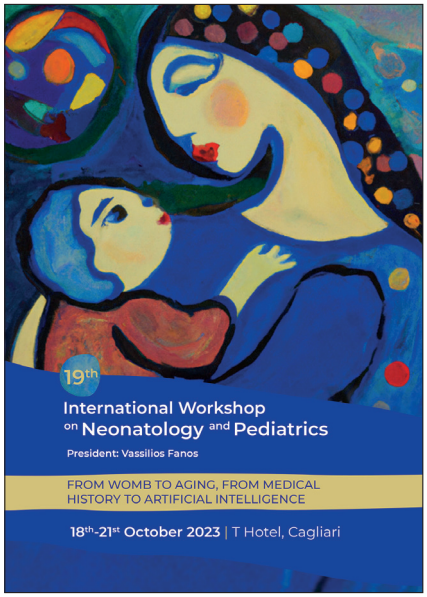

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LECT 1

NEONATAL ONSET OF GENETIC SYNDROMES

S. Giglio

Center for Research University Services, Medical Genetics Unit, University of Cagliari, Cagliari, Italy

Department of Medical Sciences and Public Health, R. Binaghi Hospital, ASL 8, Cagliari, Italy

With the growing understanding of the extent of genetic diseases in newborns and the equally rapid advancement of new technologies used for genetic diagnoses, it is critical to have a sufficient knowledge base to recognize and evaluate genetic diseases in the neonatal period. Genetic evaluation has become an essential and indispensable aspect of medicine. In recent years, much progress has been made in using massively parallel sequencing to diagnose genetic conditions in newborns rapidly. Next-generation sequencing is increasingly used for non-invasive prenatal diagnosis and is also an essential component of newborn screening.

The spectrum of malformations affecting a newborn is broad, with several hundred genetic conditions. Early diagnosis of these diverse disorders, and in particular management of inborn errors of metabolism through clinical/biochemical evaluation and newborn screening, are essential in the neonatal population to improve clinical outcomes. Craniofacial dysmorphism and/or multiple congenital anomalies, as well as neonatal hypotonia, feeding difficulties, seizures, specific congenital cardiovascular malformations, cardiomyopathy, neonatal liver disease with direct hyperbilirubinemia, cystic renal disease, structural brain defects, congenital diaphragmatic hernia, disorders of sexual differentiation and skeletal dysplasias/limb malformations, etc., suggest an underlying genetic aetiology. In all these cases, it is necessary to carry out genetic counselling to direct toward the most appropriate genetic tests. Over 4,000 Mendelian disorders are currently known to have a genetic aetiology and a significant fraction of these present in the perinatal period with one or more of these clinical presentations. While it may be difficult to clearly estimate the burden of genetic diseases presenting in the first month of life, it is notable that over 800 genetic disorders have been catalogued in the online database Mendelian Inheritance in Man, showing in the newborn period (www.omim.org).

In all these cases, the molecular diagnosis has a significant impact on the risk of recurrence for families and the provision of appropriate medical care and health interventions to the newborn. Therefore, it is essential to understand the basis of the numerous genetic tests currently applicable in clinical diagnosis and, above all, to carry them out in the shortest time and most appropriately.

LECT 2

GENETIC CHOLESTATIC LIVER DISORDERS: IS IT TIME TO CHANGE THEIR MANAGEMENT?

G. Maggiore

Hepatogastroenterology, Nutrition and Liver Transplantation, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

Genetic cholestatic disorders such as Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC), experience debilitating pruritus, for which there have been few effective treatment options. Management of these children is now changing: for the first time, new drugs, which relieve cholestatic pruritus, have been approved for use in young children with ALGS and PFIC. Maralixibat and odevixibat, ileal bile acid transporter inhibitors (IBATi), manage cholestatic pruritus in these patients, a significant step forward in improving their quality of life. Emerging data also suggest that these drugs may improve event-free survival, and their benefits may thus extend beyond symptomatic alleviation of pruritus. IBATi works by interrupting the enterohepatic circulation of bile acids. This process refers to the biliary excretion of bile acids into the small intestine, followed by intestinal reuptake of bile acids and return to the liver via the portal system. The IBAT is located at the enterocyte brush border in the terminal ileum and is responsible for the reabsorption of bile acids. IBATi, therefore, lead to increased faecal bile acid excretion and lower levels of bile acids returning to the liver. Maralixibat was approved in September 2021 in the USA and in December 2022 in the European Union

(EU) for the treatment of cholestatic pruritus in patients with ALGS over 1 year and over 2 months of age, respectively. The drug was generally well tolerated, with gastrointestinal disorders occurring in 15% of maralixibat-treated patients compared to 19% with placebo [1]. Odevixibat was approved in July 2021 in the EU and in the USA for the treatment of PFIC in patients from the age of 6 and 3 months, respectively. Results from the PEDFIC 1 and PEDFIC 2 trials were key to these approvals. PEDFIC 1 was a randomised, double-blind, phase 3 study in patients with PFIC types 1 and 2 [2]. It showed that patients treated with odevixibat experienced statistically significant improvements in pruritus compared to placebo over 24 weeks of treatment. Additionally, the percentage of patients with a serum bile acid response was higher in patients treated with odevixibat (33%) versus placebo (0%). With respect to safety and tolerability, treatment-emergent diarrhoea occurred in 31% of patients in the odevixibat group. Odevixibat has also been evaluated in patients with ALGS in the phase 3 ASSERT trial where the announced top-line data showed that it met its primary improvement in pruritus and the secondary endpoint of a reduction in serum bile acids [3]. It is notable that these drugs have been approved for use in children with cholestatic disease before approval in adults. This sets a new standard for drug development in hepatology, reversing the traditional paradigm where drugs are evaluated and approved first in adults. The IBATi have ushered in a new era in the management of pediatric cholestasis, with the prospect of improving pruritus, quality of life and transplant-free survival in patients with ALGS and PFIC. The initial clinical trials of these drugs highlight the importance of evaluating new therapies in rare paediatric diseases, not only so that these children have access to suitable drugs, but also to confirm efficacy and pave the way for new therapies for adult conditions. Long-term follow-up is needed to understand how IBATi will change the clinical trajectories currently seen in ALGS and PFIC, particularly in relation to the timing and indication for liver transplantation.

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LECT 3

WILSON DISEASE

G. Loudianos

Department of Pediatrics and Rare Diseases, Ospedale Microcitemico Antonio Cao, University of Cagliari, Cagliari, Italy

Wilson disease (WD) is an autosomal recessive disorder of copper transport characterized by reduced copper incorporation into ceruloplasmin, and by impaired copper biliary excretion. This results in progressive copper accumulation in the liver and subsequently in the brain, cornea and other tissues. The WD prevalence widely reported is of 1 in 50,000 inhabitants, while in Sardinia we estimated its prevalence in 1 in 3,000. Clinical manifestations of WD may be of any kind, but usually the symptoms of presentation are hepatic or neuropsychiatric, with a vast range of disturbances for both groups of symptoms. The hepatic clinical presentation ranges widely from asymptomatic hypertransaminasemia to cirrhosis and, less commonly, acute liver failure. Wilson's disease can also manifest with a large spectrum of symptoms, including neurological, behavioral or psychiatric disorders. The clinical hallmark of WD is the Kayser-Fleischer ring, due to copper deposition in the Descemet's membrane of the cornea. Given the large and mainly unspecific spectrum of clinical manifestations, WD should enter into the diagnosis of all patients with symptoms and signs of hepatic disease of uncertain cause in the absence of other reasons for liver disease, in all adolescents and adults with neuropsychiatric symptoms and behavioural problems of unknown origin, in all cases with the combination of both hepatic and neurological manifestations in the absence of other causes, the presence of familiarity for WD or hepatic or neurological diseases of unknown origin. The diagnosis of WD may be made easily when the classic symptoms and some laboratory findings, such as low ceruloplasmin, high 24h urinary copper, high liver copper content, are present. However, since not all the symptoms are always present, it is difficult to establish the

diagnosis, especially in children. No single test can confirm the diagnosis with 100 percent accuracy, since all routine tests for WD diagnosis can give false positive and false negative results. To improve diagnostic performance of WD, the Leipzig scoring system was proposed based on clinical biochemical, histological and molecular data that was validated in pediatric patients. WD treatment is life-long. In patients with significant chronic liver disease, treatment includes a chelator, such as penicillamine and trientine, that bound and increase renal copper elimination. Zinc is used mostly for maintenance therapy after the induction phase with chelators. The adherence to a life-long therapy may be poor, especially during adolescence. Therefore, patients should be checked periodically to supervise the occurrence of side effects and to assess adherence to the prescribed regimens.

LECT 4

HEMOLYTIC-UREMIC SYNDROME

N. Lepori[1,2], A. Atzeni[1], A. Angioi[1], M. Floris[1], G. Cabiddu[1,2], A. Pani[1,2]

[1]Universitary Department of Nephrology, Dialysis and Renal Transplantation, ARNAS "G. Brotzu", Cagliari, Italy

[2]Department of Clinical Medicine and Public Health, University of Cagliari, Cagliari, Italy

The term "thrombotic microangiopathy" (TMA) denotes a spectrum of pathological disorders characterized by diffuse thrombosis of the arterioles and capillaries of the microcirculation that affects various organs such as the kidneys, encephalon, heart, lungs and gastro-enteric tract. Various etiologies, both acquired and hereditary, are associated with TMA. Clinically, the different forms are characterized by the triad: thrombocytopenia, microangiopathic hemolytic anemia and organ damage. The classification of the various pathological entities forming part of TMA has undergone various modifications over time and is still a subject of debate in the scientific community. An initial distinction allows us to recognize primary forms of TMA (thrombotic thrombocytopenic purpura, typical hemolytic uremic syndrome, drug-induced TMA, complement-mediated TMA, TMA due to disorders of cobalamin metabolism, TMA due to coagulation factor disorders) and secondary forms of TMA (due to organ transplantation, pregnancy, neoplasia, autoimmune pathology).

Complement-mediated TMA (CM-TMA) is responsible for approximately 5-10% of the total cases of hemolytic uremic syndrome observed in individuals under 18 years of age and has a strong genetic basis. Approximately 20% of the cases of TMA historically described as an atypical hemolytic uremic syndrome (aHUS) showed a familial character and in approximately 60% of TMA cases genetic abnormalities in genes coding for complement system proteins. In approximately 5-20% of patients with CM-TMA there are acquired disorders of the complement system, in particular secondary to the development of autoantibodies against CFH.

TMA can affect any organ in which endothelial cells are present. Why the glomerular endothelium is the main target in CM-TMA remains unclear. Although the kidney is a common site of TMA, it can affect many systems and can mimic multiple pathological conditions. The central nervous system and cardiovascular system, the most affected sites of CM-TMA involvement after the kidney, are the best studied systems. The therapy of CM-TMA consists of supportive care (with a focus on the management of acute kidney injury and systemic complications) and a specific etiological treatment, centered on the use of anti-complement drugs.

LECT 5

DIAGNOSIS AND THERAPEUTIC APPROACHES TO SPINA BIFIDA: A COMPREHENSIVE REVIEW

G. Masnata

Department of Pediatric Nephro-Urology, Spina bifida Centre, Brotzu Hospital, Cagliari, Italy

INTRODUCTION

Spina bifida (SB) is a congenital neural tube defect that affects the central nervous system and spinal cord development. It is essential to make early diagnosis and a multidisciplinary therapeutic approach for optimizing patient outcomes. This scientific report provides an in-depth analysis of the diagnostic pathways and therapeutic strategies employed in the management of SB.

SB is characterized by the incomplete closure of the neural tube during embryonic development, leading to various neurological and orthopedic abnormalities. The life expectancy of patients has increased; therefore, there are some primary outcomes to achieve: to protect normal renal

function, to develop strategies for urinary continence and to promote independence in adulthood. Patients are at increased lifetime risk of chronic kidney disease due to neurogenic bladder. The application of renal protective interventions directly depends on timely detection through surveillance of renal function.

DIAGNOSTIC PATHWAYS

Prenatal screening

- Ultrasonography: routine prenatal ultrasounds can detect signs of SB as early as the first trimester;
- alpha-fetoprotein (AFP) screening.

Confirmatory diagnostic tests

- Amniocentesis: a sample of amniotic fluid can be analysed for AFP levels and genetic markers of SB;
- fetal magnetic resonance imaging (MRI) [1].

Postnatal diagnosis

- Clinical examination;
- radiological imaging: MRI is used to evaluate the extent of spinal cord involvement.

Therapeutic approaches and surgical interventions

- Closure of the spinal defect: it is performed ideally within the first 48 hours of life;
- hydrocephalus management: many patients also develop hydrocephalus, necessitating the placement of ventriculoperitoneal shunts;
- orthopedic care;
- physical therapy: it can improve muscle strength, mobility, and coordination;
- orthopedic surgeries: corrective surgeries for musculoskeletal deformities, such as scoliosis or clubfoot, are often required to enhance mobility and reduce pain.

Nephro-urological management

- Intermittent catheterization: to manage bladder dysfunction [2];
- bladder augmentation: in cases of severe bladder dysfunction, it may be necessary;
- cystatin C is also used to integrate the eGFR calculation and provide more precise kidney health and prognosis data;
- regular blood pressure monitoring and urine test strip for urine monitoring.

Neurological and developmental support

- Neuropsychological assessment: it can help identify cognitive deficits and guide educational interventions;
- early intervention programs: speech therapy, occupational therapy, and educational support are vital for optimizing developmental outcomes.

CONCLUSION

SB requires a multidisciplinary approach for diagnosis and management. Early prenatal screening and confirmatory diagnostic tests enable timely intervention, while a combination of surgical, orthopedic, urological, and developmental therapies enhances the quality of life [3].

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LECT 6

NEUROLOGICAL MANIFESTATIONS OF NEUROFIBROMATOSIS TYPE 1

C. Soddu

Department of Pediatrics and Rare Diseases, P.O. Microcitemico "A. Cao", Cagliari, Italy

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by mutations in the *NF1* gene, which result in defective function of its gene product, neurofibromin. The clinical manifestations of NF1 are extremely heterogeneous, even amongst people of the same family. The underlying mechanisms have not yet been fully clarified.

The most common signs and symptoms of NF1 include neurofibromas as well as the appearance of harmless café au lait spots. However, the disease predisposes patients to the development of tumors, with a 5-15% increased risk compared to the general population. With its progressive and unpredictable course, NF1 can affect many different organs and systems, but effects on the nervous system are a defining feature. Central and peripheral nervous system manifestations include structural, functional, and neoplastic alterations. Up to 70% of children affected by this disease manifest learning difficulties, attention deficits and behavioral problems. NF1 is also associated with

higher seizure frequency compared to the general population, with a prevalence of about 5%. Focal areas of signal intensity – non-neoplastic lesions of the central nervous system – are present in most patients without clear clinical correlation. Obstructive hydrocephalus occurs in ≤ 13% of patients, and may arise secondary to tumoral or nontumoral causes. Children with NF1 can present with progressive arteriopathy of the branches of the internal carotid artery consistent with Moyamoya syndrome (MMS). MMS may manifest with ischemic and hemorrhagic cerebrovascular events, but is most frequently asymptomatic and therefore underestimated.

Neoplasms have heterogeneous morphological features and biological potential: central nervous system gliomas and neurofibromas are the most common tumors; malignant gliomas and malignant peripheral nerve sheath tumors represent the two most common causes of tumor-related mortality in patients with NF1.

CONCLUSIONS

NF1 is a complex multiorgan disease primarily and pervasively affecting the nervous system. The pathogenesis, prevalence and natural history of neuro-oncological complications have yet to be fully elucidated. Its clinical presentation can be variable and very insidious, thus requiring early genetic and clinical evaluation, targeted investigations, and individualized follow-up program.

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LECT 7

SYDENHAM'S CHOREA: UPDATE ON DIAGNOSIS AND THERAPY

T. Foiadelli

Pediatric Clinic, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Sydenham's chorea (SC) is the most common cause of acute acquired chorea in childhood. SC is a hyperkinetic movement disorder associated with neuropsychiatric manifestations. It is a neuroimmune disorder, caused by an inflammatory autoimmune response following a group A beta-hemolytic streptococcal pharyngitis, and it is one of the major diagnostic criteria for acute rheumatic fever diagnosis. SC has long been considered a relatively benign and self-limiting disease; however, the social and functional burden of SC can be high, more than half of the patients have disabling psychiatric symptoms that may persist after the motor symptoms have resolved, and up to 10% of the patients may experience a clinical relapse. Despite the fact that it has been described centuries ago, both diagnostic biomarkers and evidence-based therapeutic guidelines for SC treatment are still lacking. In fact, the diagnosis of SC remains clinical, and the management of the neurological and psychiatric complications is left to physicians' clinical experience. Therapy of SC relies on three major pillars: antibiotic treatment and prophylaxis, symptomatic antichoreic drugs, and immunomodulatory treatments. Symptomatic drugs (e.g., valproic acid, haloperidol, pimozide, etc.) are usually effective in controlling the choreic movements but have potentially severe side effects and scarce efficacy in terms of long-term prognosis (with a recent alert regarding the possibility of a higher relapse risk). Immunomodulatory treatments (e.g., steroids and IVIG) have recently been reported to be faster and possibly more effective, but should be only used in the more severe cases. To conclude, the therapeutic heterogeneities reflect the severe gap of knowledge that concerns SC's pathogenesis and manifestations, and the importance of a standardized clinical assessment and high-quality research studies in this field should be stressed.

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LECT 8

EPILEPTIC ENCEPHALOPATHIES

D. Pruna[1], S. Cossu[1], M. Asunis[1], S. Dettori[1], F. Banditelli[2], M. Balzarini[3]

[1]*Child Neurology and Epileptology Unit, ASL Cagliari/ARNAS Brotzu, Cagliari, Italy*

[2]*Childhood and Adolescence Neuropsychiatry Clinic, Cagliari University, Cagliari, Italy*

[3]*Pediatric Unit, ARNAS Brotzu, Cagliari, Italy*

The term "epileptic encephalopathy" (EE) was defined by the ILAE report as where the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone. Global or selective impairments can worsen over time, encompass a spectrum of severity across all epilepsies, and can occur at any age. Many epilepsy syndromes associated with encephalopathy have a genetic etiology or may have an acquired cause, such as hypoxic-ischemic encephalopathy or stroke, or may be associated with a malformation of cortical development. In an EE, the abundant epileptiform activity interferes with development, resulting in cognitive slowing and often regression, and sometimes is associated with psychiatric and behavioral consequences. Many of these severe genetic disorders also have developmental consequences arising directly from the effect of the genetic mutation, in addition to the effect of the frequent epileptic activity on development. In conditions where the cognitive development and behavior are impaired independently of the epilepsy onset, and epilepsy is characterized by a high frequency of seizures and abundant epileptiform abnormalities, the term "developmental and epileptic encephalopathy" (DEE) is more appropriate. In most cases of DEE, epilepsy onset and developmental impairment are seen very early in life. The term "developmental encephalopathy" (DE) should be used where there is just developmental impairment without frequent epileptic activity associated with regression or further slowing of development; EE where there is no preexisting developmental delay and the genetic mutation is not thought to cause slowing in its own right; and DEE where both factors play a role [1]. Patients with EE require aggressive antiseizure interventions. In this setting, suppression of seizures and epileptiform abnormalities of the EEG might lead to an improvement in cognitive function, although not necessarily a return to normal function. Furthermore, the underlying etiology remains key to the long-term outcome. Whilst attaining control of the typically refractory seizures may be challenging, treatment is still indicated for safety and quality of life [2]. Development of diagnostics and efficient diagnostic protocols is vital for the treatment plan and to assure prognosis. In genetic DEE, the value of newly discovered genetic variants is not always fully known, and validation with functional studies is still required for many newly discovered genes. Validated tools are also needed to formulate solid genotype-phenotype correlations that can be used in clinical management [3].

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LECT 9

SYNDROMIC DEAFNESS

S. Savasta

Department of Pediatrics and Rare Diseases, "Microcitemico" Hospital, Cagliari, Italy

Department of Clinical Medicine and Public Health, University of Cagliari, Cagliari, Italy

Syndromic deafness represents only a small percentage of child deafness (10-15) and a little-known, probably lower, percentage of adult deafness. Deafness represents the most frequent sensory defect and occurs at birth with a frequency of 1/1,000 newborns. Deafness can be determined by both genetic and environmental factors. It may be a consequence of perinatal infections, acoustic or brain trauma and the use of ototoxic drugs. In 60% of cases, it is of genetic origin. Among the genetic forms, syndromic forms are recognized (30%). The deafness may be the only sign present or may be accompanied by other signs and symptoms, as in syndromic forms. To date, several hundred deafness

syndromes have been described and more than 220 genes for hearing loss have been identified. In syndromic deafness, there are other signs and/or symptoms that define some fairly common conditions, such as Usher syndrome (USH) and Pendred syndrome, Alport syndrome, Wanderburg syndrome. Two of these are autosomal recessive and initially present with isolated deafness and are relatively frequent among the syndromic forms of deafness: USH and Pendred syndrome. USH is characterized by degenerative vision loss known as retinitis pigmentosa (RP), sensorineural hearing loss, and vestibular dysfunction. RP can cause degeneration and the loss of rod and cone photoreceptors, leading to structural and functional changes in the retina. Type I (USH1) is characterized by a congenital, severe-to-profound deafness and absent vestibular function. Type II (USH2) shows congenital and moderate-to-severe hearing loss and normal vestibular response. A third type (USH3) is also suggested, clinically similar to USH2, but with progressive hearing loss. The genetic heterogeneity of USH is quite extensive. Up to now, 7 different loci responsible for the defect are known: 14q, 11q, 11p, 10q and 21q for USH1; 1q for USH2 and 3q for USH3. Pendred syndrome is an autosomal recessive disorder characterized by sensorineural hearing loss, inner ear malformations, goiter, and abnormal organification of iodide. It is caused by mutations in *SLC26A4* gene, which encodes the multifunctional anion exchanger pendrin. Pendrin has affinity for chloride, iodide, and bicarbonate, among other anions. In the inner ear, pendrin functions as a chloride/bicarbonate exchanger that is essential for maintaining the composition and the potential of the endolymph. In the last few years, rare conditions involving deafness have been reported, such as macrothrombocytopenia, heterogeneous disorders group characterized by thrombocytopenia and giant cells and which also include other clinical signs and laboratory such as hereditary nephritis and sensorineural hearing loss and cataract. The most recent discoveries in molecular genetics have demonstrated different mutations of the gene 9 (*MYH9*), which codes for the IIA, an heavy chain of non-muscular myosin. Another group of hypoacoustic syndromes is made up of an original association between sensorineural hearing loss, hypoplasia of the tooth enamel and chromatic anomalies of the nails, as in Hamler syndrome. These new syndromic pictures suggest the importance of not limiting oneself to audio-phonological diagnosis, but of implementing multi-disciplinary clinical-diagnostic protocols. However, it is important to recognize and research the main syndromes because the management and etiological outcome are different compared to non-syndromic deafness.

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LECT 10

METABOLIC MYOPATHIES

M. Balzarini

Pediatric Department, "S. Michele" Hospital ARNAS Brotzu, Cagliari, Italy

Metabolic myopathies (MM) are a wide class of diseases caused by impaired substrate use in muscles. They can be secondary to acquired conditions such as hypothyroidism, statin use or vitamin D deficiency, or primarily caused by a genetic defect in one metabolic pathway, such as carbohydrate metabolism, lipids metabolism or mitochondrial and respiratory chain metabolism [1].

Several disorders of glycolysis and glycogenolysis can cause muscle disease, with or without hepatic involvement. The most common, GSD V or Mc Ardle disease, is characterized by exercise intolerance manifested by rapid fatigue, myalgia, and cramps in exercising muscles. It can be suspected in case of second wind phenomenon, consisting in relief of myalgia and rapid fatigue after a few minutes of rest. In glycogen metabolism diseases, the symptoms usually arise within the first two seconds to minutes of exercise or when the intensity increases beyond the anaerobic threshold [1, 2].

Another class of MM is caused by dysfunction in lipids metabolism. They present with symptoms in long-duration exercise, after prolonged fasting, or in the event of stressful conditions (such as fever, infections, starvation, steroid therapy). Clinical presentation is variable, ranging from proximal myopathy and exercise-induced myalgia to rhabdomyolysis, cardiomyopathy and multiorgan failure. In beta-oxidation defects, patients show alteration in acylcarnitine profile and sometimes organic urinary

acids (to be collected during the acute phase), and can present hypoketotic hypoglycemia. In case of recurrent rhabdomyolysis in children under 6 years of age, the differential diagnosis must include carnitine palmitoyltransferase deficiency (CPT2), the most frequent beta-oxidation defect, and LPIN1 deficiency, a phosphatase involved in lipid homeostasis. Both conditions can cause severe CK elevation and lead to renal failure and cardiac arrhythmias if not promptly treated [3].

The last category are defects in respiratory electron chain function. Mitochondrial cytopathies show a broad range of phenotypic or genotypic heterogeneity. Suspicion of mitochondrial myopathy should arise in case of multisystemic involvement, fixed weakness, lactate and alanine elevation, ptosis, diabetes, hypoacusia, or psychomotor regression in infants [2]. These diseases can benefit from cofactor supplementation (Q10, thiamin, riboflavin, biotin), but their therapy remains mainly symptomatic.

The diagnosis of MM relies to date on targeted NGS sequencing panels of nuclear or mitochondrial genome and, in some cases, on whole exome sequencing (WES), guided by clinical suspicion and biochemical data. Muscle biopsy can be useful in case of unsolved or dubious diagnosis, in the need of muscle DNA extraction or respiratory chain complex analysis [2]. As for all metabolic diseases, an early diagnosis can modify the prognosis of several treatable conditions, and therefore must be pursued punctually.

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LECT 11

PREVIEWS OF THE MILCH STUDY IN A CHANGING PLANET

P. Palanza[1], V. Fanos[2], A.M. Papini[3], M.E. Street[1,4]

[1]*Department of Medicine and Surgery, University of Parma, Parma, Italy*

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

[3]*PeptLab-MODELS, Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Italy*

[4]*Unit of Pediatrics, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy*

Breastmilk is the best nutrition source for infants and it is potentially exposed to environmental pollutants, including endocrine-disrupting chemicals (EDCs). EDCs are man-made chemicals present in everyday-life environment that can disrupt the programming of endocrine signaling pathways during development, resulting in adverse effects later in life. The ongoing European LIFE-MILCH project (www.lifemilch.eu) is a longitudinal study that aims to determine the association between levels of maternal milk exposure to EDCs and infants' physiological and neurobehavioral development in the first year of life in two Italian regions, Emilia Romagna and Sardinia, in order to establish a risk assessment model of maternal nutritional and life habits, EDC levels and their effects on infant health and development. Based upon the risk assessment model, the project aims to establish safety guidelines to reduce maternal and infant exposure to EDCs and to assess their efficacy in a follow-up study.

In the 3 recruitment centers (Parma, Reggio Emilia and Cagliari), 654 mother-infant dyads were enrolled. The mothers were enrolled at 36-40 weeks of gestation. All women filled questionnaires related to life and nutritional habits at enrolment, birth, 1, 3, 6, and 12 months after delivery. The duration and type of lactation was registered. At any time-point, infants were evaluated for growth and anthropometric measurements, pubertal stage, anogenital distance (AGD), subcutaneous adiposity; neurobehavioral development was assessed by different tests: Visual Preference Paradigm (1 month), Face-to-Face-Still-Face (3 month), Fagan Test (6 month), Barrier Task (12 month), and the Bayley III Scale (6 and 12 months). At any time-point, biological samples (maternal and infant urine and breastmilk) were obtained and then analysed for EDCs levels.

Preliminary results show that maternal nutrition during pregnancy and lactation has effects mostly on weight and distribution of fat in infants, on the clinical signs of minipuberty, on AGD and on emotional responses. A preliminary analysis on a subset of data shows significant interaction effects between pre- and post-natal bisphenols and parabens concentration levels in breastmilk and maternal urine with infant growth and neurodevelopment parameters. More specifically, effects on AGD, body weight, socioemotional stress response, and

specific neurodevelopmental areas were found. These preliminary results suggest that infant early physiological and neurobehavioral outcomes may be affected by exposure to EDCs and may provide early biomarkers of effects in relation to maternal lifestyle and nutritional habits.

ACKNOWLEDGMENT

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LECT 12

THE FIRST COMPREHENSIVE DIAGNOSTIC PROFILE OF SPECIFIC METABOLITES OF EDCs (PHTHALATES, BISPHENOLS, PARABENS, PYRETHROIDS, PAHS, AND POLAR PESTICIDES) IN MOTHER AND CHILD DYADS: NEWS FROM THE LIFE MILCH PROJECT

F.R. Fernandez[1], F. Nuti[1], P. Palanza[2], M.E. Street[2,3], V. Fanos[4], A.M. Papini[1]

[1]Laboratory of Molecular Diagnostics & Life Sciences MoD&LS-PeptLab, Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Italy

[2]Department of Medicine and Surgery, University of Parma, Parma, Italy

[3]Unit of Pediatrics, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy

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

Endocrine-disrupting chemicals (EDCs) are exogenous substances ubiquitous in everyday life. In fact, they are extensively used in different industrial processes, such as plasticizers in plastics and/or in food storage materials, in children's products, in cosmetic and pharmaceutical preservatives, in industrial solvents and their byproducts, in agriculture. EDCs are a group of substances highly heterogeneous that "interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones also at very low concentration in an intact organism" [1, 2]. The screening of the different EDCs in biological fluids of the mother-child couple can be essential to understand the impact of EDCs on health of infants (general health status, cognitive development, metabolic regulation, development of intolerances and allergies, etc.).

Furthermore, the effect of monitoring the presence of EDCs in biological fluids can help the community to develop a correct "risk perception" of diseases among citizens and lead to the implementation of good eating and living practices. Therefore, the screening of EDCs in mother-child dyads can increase knowledge concerning correlation between exposure and damage to health, also helping the EU to improve the know-how on multiple exposures and cumulative effects. This is the final aim of the Life MILCH project [3-6] (LIFE18 ENV/IT/000460, https://lifemilch.eu/en/progetto.html). Considering our previous experience [3], we propose a series of sensitive and rapid methods for measuring EDCs levels in mother's and child's biological fluids, such as urine and serum, breast milk, but also in infant formula and baby bottles.

Six UPLC-MS/MS methodologies were set up to analyse a total of 42 chemicals:

- group A: 4 bisphenols (bisphenols A, S, F and bisphenol F 1,1'-[methylenebis(4,1-phenyleneoxy)]bis[3-chloro-2-propanol]);
- group B: 7 parabens (methyl, ethyl, propyl, isopropyl, butyl, isobuthyl and benzyl esters of parahydroxybenzoic acid);
- group C: 11 polycyclic aromatic hydrocarbons (PAHs, anthracene, pyrene, phenantrene, chrysene, benz(a)anthracene, benzofluoroanthracene + benzo(a)pyrene + benzo(k)fluoranthene, benzo(ghi)perylene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene);
- group D: 4 pesticides (chlorpyrifos, glyphosate and its major metabolites glufosinate and aminomethylphosphonic acid);
- group E: 14 phthalates (dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzyl butyl phthalate, di-n-octyl phthalate, di-(2-ethylhexyl)phthalate, mono-methyl phthalate, mono-ethyl phthalate, mono-n-butyl phthalate, mono-benzyl phthalate, mono-n-octyl phthalate, mono(2-ethylhexyl)-phthalate, mono(2-ethyl-5-hydroxyhexyl)-phthalate, mono(2-ethyl-5-oxohexyl)- phthalate);
- group F: 2 pyrethroid insecticides (cypermethrin and cyfluthrin).

These methods were applied to longitudinally monitor 122 mother-child dyads and, in particular, to the quantification of EDCs in the abovementioned biological fluids and in commercially available baby bottles and infant formula. A risk assessment model including lifestyle and maternal EDCs burden is under development, taking into consideration two main end-points: 1) how maternal lifestyle and nutritional habits may affect the level of EDCs in breast milk and 2) the levels of EDCs in the designed biomonitoring study.

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LECT 13

THE IMPACT OF ENDOCRINE DISRUPTORS: WHICH CONSEQUENCES?

M.E Street[1,2], P. Palanza[1], V. Fanos[3], A.M. Papini[4]

[1]Department of Medicine and Surgery, University of Parma, Italy
[2]Unit of Paediatrics, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[3]Department of Surgical Sciences, University of Cagliari, Italy
[4]Laboratory of Molecular Diagnostics & Life Sciences MoD&LS-PeptLab, Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Italy

Currently, we live in the era described as the Anthropocene. Humans have synthesized over 80,000 chemicals. Of these a number act as endocrine-disrupting chemicals (EDCs). By definition, an EDC is an "endocrine active substances that can interact or interfere with normal hormonal action". When this leads to adverse effects, they are called endocrine disruptors. EDCs are found in food, and food containers, in fabrics, in all plastic containers, in electronic devices, in medical equipment, in packaging, and so forth.

The action in humans is difficult to describe, and most studies are large epidemiologic studies, but effects in nature, *in vivo* and *in vitro* have shown how these chemicals work and how they can negatively affect neurodevelopment, immune defenses, processes related to growth, including effects on bone, and fertility. If exposure is *in utero*, the effects are mainly mediated by epigenetic changes in gene regulation affecting future health during life and the risk of non-communicable diseases. Thereafter, one can observe developmental effects, and in adulthood the endocrine effects are more evident. Exposure is by ingestion, contact and inhalation. EDCs can interfere with hormone synthesis, secretion and action acting both as agonists and antagonists. Each individual has a personal exposure and response to these exogenous chemicals (resposome and exposome); thus, the effect can be different. Moreover, there are critical windows of exposure for all *in utero* life, infancy and puberty. One must also keep in mind that there is not a linear dose response to exposure, and that the effect of a single EDC is different from that of a mixture as occurs in everyday life [1, 2].

The current lines of evidence have shown effects on neurodevelopment, with effects becoming evident towards school age. Interestingly, the increase in the production of chemicals parallels the increase in autism. Some EDCs have several effects on adipose tissue (obesogenic effect). Studies have shown that they are able to: increase number and size of adipocytes, alter hormone regulation of satiety, appetite and food preference, alter fat metabolism, metabolic rate and calorie storage, energy balance and insulin sensitivity.

At the level of the insulin islet cells, effects favoring the onset of diabetes mellitus have been shown. Finally, some of the disruption is also related to changes in the microbiome.

Growth and longitudinal bone growth and quality of bone have also been shown to be affected through many mechanisms [3]. Exposure *in utero* to some pollutants is associated with low birth weight, and a ecologically short stature is being hypothesized. After birth, exposure is through breast milk, although some EDCs have been recently traced in formula milk, as well. It is of upmost importance to "protect" breast milk, being the optimal source of nourishment at birth.

Awareness of EDCs is important to reduce exposure. Currently, the LIFE-Milch European project, ongoing in Italy, is assessing exposure to many EDCs in mothers at the end of pregnancy, in mother-newborn/infant pairs up the 12 months of life, with

a special focus on breastmilk, neurodevelopment, growth, distribution of adiposity, and effect on pubertal stages, and anogenital distances as a measure of estrogen and/or androgen action. A risk model is under development.

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LECT 14

PLASTIC AND BREASTFEEDING

A. Ragusa

Department of Obstetrics and Gynecology, Università Campus Bio Medico di Roma, Rome, Italy

8,300 million metric tons of virgin plastics have been produced until 2017, and plastic production continues to increase. Up to 50% of that is for single-use purposes, utilized for just a few moments. Few years ago, we demonstrated the presence of microplastics (MPs) in the human placenta and in human milk, but what health concerns could MPs pose for infants?

In humans, we do not yet have definitive evidence of toxic effects of MPs. However, there is very clear evidence in experimental animals that MPs and nanoplastics (MNPs) that enter the body through respiration, skin, and gastrointestinal tract, reach all the main tissues, organs, and systems, where they can determine toxic and harmful effects.

We absolutely need conscious citizens to elect politicians who can lead change. Nothing to say, therefore, about individual ecological choices, but we cannot ignore the choices of global politics.

The initial decalogue to address the problem could be the following:

1. sign international agreements to reduce the production of virgin plastic;
2. give the responsibility and costs of plastic producers for its disposal;
3. gradually replace plastic with recyclable material of natural origin;
4. increase the recycling rate of plastic materials;
5. ban the sale of mineral water and carbonated soft drinks in plastic containers and abolish the use and production of single-use plastics (straws, bags, plates, cutlery, and plastic cups);
6. use organic materials for packaging;
7. produce natural plastic with algae, potatoes, corn, etc.;
8. buy bulk and non-plastic packaged foods;
9. buy clothing made from natural and non-synthetic materials;
10. teach all this in schools.

MPs were widely found also in milk powder, and boxed formula powder has more plastic pollution than canned formula powder. The boxed baby formula powder mostly had inner linings made of polyethylene plastic and aluminum foil. The use of commercially available single-use breastmilk storage bags determines the ingestion by infants of MPs and other particles, ingested by infants from the use of breastmilk storage bags. The quantity was estimated to be 0.61-0.89 mg/day based on the average daily breastmilk intake by infants. In addition, MP exposure from feeding bottles is 6.8 times higher than that from milk powder, and milk powder preparation is 1.7 times higher. More babies-focused research has estimated that a single baby intake of MPs from bottles is between 14,600 and 4,550,000 particles/day, with the lowest levels observed in Africa and Asia. When shaken with hot water, plastic bottles release up to 16 million MPs per liter and that sterilization and high-temperature water significantly increased the release of MPs. Overall, they concluded that babies fed plastic bottles will be exposed to 14,600-4,550,000 particles/day. Ultimately, the milk contained in these artificial containers is much richer in MPs than breast milk and does not even have the same healthy characteristics as breast milk, for example all antibodies, for which women must be absolutely advised against using this type of artificial milk, unless it is necessary; despite the presence of MPs, breast milk remains the ideal food for newborns. Briefly: breast milk, despite the presence of MNPs is the best source of nutrition for most babies.

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LECT 15

THE CRISIS IN THE CRITICAL SITUATION

E.M. Oppedisano[1], G. Melis[2], F. Sau[2], G. Cherchi[2]

[1]School of Pediatrics, University of Cagliari, Cagliari, Italy

[2]Department of Pediatric Emergency and Urgency Care, Brotzu Hospital, Cagliari, Italy

INTRODUCTION

Status epilepticus is a medical emergency that causes risk of death or permanent neurological injury. For a patient who arrives to the Emergency Department with ongoing seizures, since it is difficult to exactly establish the timing of the onset, a condition of status epilepticus must be considered. Pharmacological treatment must be started early, as the duration of the seizures is a prognostic factor for the effectiveness of the therapy and the reduction of complications [1]. In managing a red code, the teamwork of the Emergency Team is of fundamental importance [2].

CASE REPORT

T. is a 10-year-old girl with neonatal hypoxic-ischemic encephalopathy, with outcomes of hypotonic tetraparesis and absence of head and trunk control, drug-resistant epilepsy and bilateral blindness. She arrived with code red at the pediatric emergency room accompanied by the 118 ambulance, with her mother who reported an increase in seizures in the last 4 days; that same morning, the crises would have begun to take on an incoming character, and the mother would have administered midazolam 10 mg at home at 6:00 am.

ABCDE examination shows:

A. pervious and maintainable airways, presence of secretions;
B. mild dyspnea, SpO_2 70% in room air, breath sounds discreetly transmitted bilaterally, increased respiratory rate;
C. valid and rhythmic heart sounds, HR 120 bpm, PA 110/70 mmHg, pale skin, warm ends, refill 3", normosphygmic peripheral pulse;
D. epileptic seizure with stiffening of trunk and limbs, head diversion with horizontal nystagmus, normal reaction of the pupils to light;
E. apyrexia, normal pharynx, abundant oral secretions, macroglossia.

Remaining findings: normal.

First, the secretions were aspirated from the airways and O_2-therapy was started, with gradual improvement in saturation; the nursing staff positioned IV access. A monitor was placed, and an EKG was performed, which showed no alterations. This seizure resolved itself spontaneously. A few minutes later, a new seizure occurred, for which a bolus of midazolam 5 mg IV was administered (0.2 mg/kg); subsequently midazolam infusion was started at the rate of 0.05 mg/kg/h. Vital parameters remained stable. The pediatric anesthesiologist was alerted. However, in a matter of a few more minutes, the child started to desaturate and went into respiratory arrest. The pediatric anesthesiologist intubated the child, after administering anesthetic drugs, and the child was transferred to the Intensive Care Unit (ICU). T. remained hospitalized in the ICU for 42 days. During her stay in the ICU she underwent a tracheostomy. She was hospitalized at Brotzu Hospital, in the Pediatrics Ward, for 20 days, with a diagnosis at discharge of "respiratory failure, status epilepticus, bilateral pneumonia". Now she is stable in her criticality.

CONCLUSION

There is no standardized treatment schedule for status epilepticus. There are a number of evidence-based guidelines that differ, particularly on second-tier medications. Nevertheless, there is a common agreement on initial management, especially life support:

- alert the resuscitator;
- continuously monitor vital parameters (TC, RR, HR, SaO_2, BP), state of consciousness (GCS or AVPU) and diuresis;
- protect airways (suction secretions, Guedell, AMBU), O_2-therapy (100%);
- place IV/IO vascular access and support circulation;
- sample for: ABG (arterial blood gases), Na, K, Ca, Mg, blood sugar, CRP, blood urea nitrogen, creatinine, anti-epileptic drug dosage (if the patient is being treated) in order to identify and treat cases of hypoglycemia, hypovolemia, electrolyte imbalance, acidosis, fever.

Prefer IV midazolam as first level drug, in bolus, repeatable up to once if no response is obtained [3-6]. Then switch to second level drugs (valproic acid, levetiracetam, lacosamide, phenobarbital, midazolam in continuous infusion) [3-6]. Third level of assistance, according to the guidelines, are based on orotracheal intubation, the use of anesthetic drugs with specialist management by anesthesiologists and/or neurologists, EEG monitoring, hospitalization in ICUs [3-6].

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LECT 16

AN UNUSUAL DYSPNEA, NEVER FALL FOR A DIAGNOSIS

M. Casadio[1], G. Colucci[2], G. Cherchi[3]

[1]*School of Pediatrics, University of Cagliari, Italy*

[2]*Department of Pediatrics Emergency and Urgency Care, Brotzu Hospital, Cagliari, Italy*

INTRODUCTION

Numerous conditions can be responsible for acute dyspnea in children; some can be life-threatening and require a rapid medical intervention. After assessing the severity of the condition and restoring proper oxygenation, it is necessary to establish the cause and perform a differential diagnosis.

CASE REPORT

A 3-month-old male infant shows up at the Pediatric Emergency Department pale, tachy-dyspneic, tachycardic and with reduced appetite for approximately 24 hours. The medical history was unremarkable, the pregnancy was uncomplicated, and there were no issues reported during fetal ultrasounds. In the physical examination, retractions are noted at the jugular, intercostal and subcostal areas. Upon chest auscultation, breath sounds are decreased on the left side. Following initial stabilization with oxygen administration, aerosol therapy with adrenaline and salbutamol, high-flow oxygen therapy is initiated. Suspecting atelectasis due to bronchiolitis, a chest X-ray is performed, revealing homogeneous opacity in the left hemithorax, likely related to pleural effusion. At the Pediatric Ward, a chest CT scan reveals a substantial solid mass occupying the middle and lower left lung fields, causing contralateral mediastinal deviation. Due to worsening respiratory insufficiency, the patient is transferred to the Intensive Care Unit, intubated, connected to a mechanical ventilator, and sedated. After placing a nasogastric tube and central venous catheter, a chest X-ray shows basal air bubbles. A chest and abdominal CT scan with contrast confirms the diagnosis of a large posterior left-sided diaphragmatic hernia with displaced ileal and colic loops in the thorax and anteriorized spleen. The child is transferred to a Tier-Three Center to reduce abdominal viscera and correct the diaphragmatic defect.

CONCLUSIONS

Congenital diaphragmatic hernia is a malformation characterized by incomplete or absent diaphragm formation, resulting in abdominal viscera herniation into the thorax. Diagnosis is often made through routine prenatal ultrasound screening between the 18th and 22nd weeks of gestation [1]. Despite advanced instrumental technology, congenital malformations of this nature may remain unnoticed during fetal life and become evident many months after birth. This leads to interindividual variability and diagnostic delay and should be suspected in cases of respiratory or gastrointestinal symptoms of unknown origin, both acute and chronic. Proper treatment involves endotracheal intubation and mechanical ventilation, avoiding mask ventilation to prevent gastric distention and lung compression, followed by nasogastric tube insertion to decompress the intestine [2]. Despite increased survival and reduced mortality rates over time, secondary morbidity has risen. Thus, long-term thorough follow-up is necessary for the early detection and timely treatment of acute and delayed complications [2].

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LECT 17

BEWARE OF THE CAT

G. Casti[1], S. Marras[2], R. Basile[2], M. Zanda[3], G. Cherchi[2]

[1]*School of Pediatrics, University of Cagliari, Cagliari, Italy*

[2]*Pediatric Emergency Room, ARNAS G. Brotzu, Cagliari, Italy*

[3]*Pediatric Department, ARNAS G. Brotzu, Cagliari, Italy*

INTRODUCTION

Bartonella henselae (*B. henselae*) is an infectious cause of encephalopathy. The mechanism is unclear and the clinical presentation may be similar to encephalitis.

CASE REPORT

An 8-year-old girl, who has previously consulted for left, cervical lymphadenitis, abdominal pain and multiple, hypoechoic, splenic lesions, comes to the Pediatric Emergency Department for a convulsive status epilepticus associated with fever. The Emergency Unit follows the department's protocol: they promptly take the patient's vital signs, examine her, place a peripheral intravenous line, perform the first blood tests, and stabilize the patient with antiepileptic medications (midazolam, then levetiracetam). After the immediate supportive care, she is hospitalised in the Pediatric Department, where she undergoes the first diagnostic tests and where an empiric treatment with ceftriaxone and acyclovir is started. The electroencephalogram shows a pattern compatible with encephalitis and the diagnostic tests reveal positive IgM and IgG for *B. henselae*. The other performed tests are negative. The diagnosis of cat scratch disease (CSD) encephalopathy leads to modify the therapy, to discontinue acyclovir and ceftriaxone and to start azithromycin and rifampin, with complete patient recovery.

CONCLUSION

CSD is an infectious disease that it is most often caused by *B. henselae*, a Gram-negative rod, whose main reservoir is the cat. The clinical manifestations include lymphadenopathy, visceral organ involvement, fever of unknown origin, neurologic manifestations, such as encephalic involvement, and others [1]. Even if the possibility of neurologic involvement in patients with CSD is widely accepted, the pathophysiologic mechanisms are still unclear. The clinical overlap between encephalitis (the inflammation of the brain parenchyma associated with neurologic dysfunction) and encephalopathy (an altered mental status associated or not with an inflammation of the brain tissue) makes it even more difficult [2]. In the *Consensus statement* of the International Encephalitis Consortium, *B. henselae* is recognized as a cause of encephalopathy without inflammation [2]. The similar clinical state obliges to always consider the possibility of encephalitis caused by another agent. To avoid the underestimation of the diagnosis of encephalitis and to help in clinical practice, the above-mentioned *Consensus statement* [2] overcomes this problem by identifying the same diagnostic criteria for both encephalitis and encephalopathy of presumed infectious or autoimmune etiology. This ensures that diagnostic tests and empiric treatments are started as soon as possible, and the latter are modified once an etiological diagnosis has been confirmed.

REFERENCES

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