2853 cm⁻¹, as biomarkers of apoptosis, were assessed.

Our in vitro biological screening system detected embryotoxic/anti-tumor impact of both HDIs. FTIR spectroscopy was able to discern biomarkers of histone acetylation and apoptosis in spent media metabolomes, thus upgrading our biological in vitro system for faster screening of embryotoxic/antitumor agents.

84 RARE COPY NUMBER VARIANTS IN CONGENITAL HEART DEFECTS

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To detect copy number variants (CNVs) in patients with congenital heart defects (CHD) and identify potential novel candidate genes involved in CHD pathogenesis. CHD are the most common congenital anomalies. Etiology of CHD can be genetic (chromosomal abnormalities, rare single gene disorders) or environmental, but it is mostly multifactorial. Copy number variants (CNVs) are important causes of genetic syndromes associated with CHD. Chromosomal microarray (CMA) is used as the first test to detect the CNVs in this category of patients.

We have evaluated 260 subjects with CHD in the period between Jan 2016 and Sep 2019 using CMA. In the majority of cases additional features such as facial dysmorphism, intellectual disability/developmental delays (ID/DD) or extracardiac anomalies (ECA) (190/260; 73.1%) were present; the remainder had isolated CHD. CMA analysis was performed using Agilent SurePrint G3 Unrestricted CGH ISCA v2 Human Genome, 8x60 K oligonucleotide microarray format according to the manufacturers' instructions (Agilent Technologies, USA).

Copy number variants were detected in 71 (71/260, 27.3%) patients; 53 of them (53/71, 74.6%) were classified as pathogenic and 18 (18/71, 25.4%) as variants of unknown clinical significance (VUS). Pathogenic CNVs were predominantly deletions (36), followed by duplications (9) and complex rearrangements (8). CNVs were discovered in 4 patients with isolated CHD (4/70, 5.7%) and 67 patients with additional feature/s (67/190; 35.3%). The most frequent pathogenic CNV was 22q11.21 deletion (DiGeorge syndrome), followed by other well-known syndromes (Williams, 5p deletion etc.). Beside these, we detected CNV clusters in loci that have previously been associated with CHD in literature (such as 15q11.2, 8p23.1, 1q43 etc.). We also observed rare CNVs in loci that have not yet been recognized as important in CHD pathogenesis (i.e. Yp11.2, 17q24, 15q24.3 etc.) Identification of rare CNVs is important for clarification of CHD pathogenesis. Potential novel candidate genes in these loci warrant further research.

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85 CLINICAL, CYTOGENETIC AND MOLECULAR FINDINGS IN PATIENTS WITH PALLISTER-KILLIAN SYNDROME

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Goal Pallister Killian syndrome is a rare genetic disorder caused by tissue-limited mosaicism tetrasomy of the short arm of chromosome 12, which usually presents as an extra isochromosome 12p. Clinical features include distinct facial anomalies, other systemic abnormalities with variable developmental delay and intellectual impairment. The aim of this work is to present clinical and cytogenetic findings of PKS patients diagnosed in our Clinic for the last 12 years and to compare their findings with previously published cases.

Methods The suspicion of PKS was set after the recognition of their characteristic phenotypic features. The diagnosis was confirmed by karyotype analysis of fibroblast cultures and In situ hybridization with chromosome 12-specific DNA, which revealed the supernumerary mosaic i(12p).

Results Since 2008 four patients with PKS were diagnosed and treated at our Clinic. Karyotypes obtained from cultured peripheral lymphocytes were normal in two cases, while karyotypes obtained from cultured skin samples revealed the supernumerary mosaic i(12p) in all four patients.

Conclusion The wide phenotypic spectrum of PKS in conjunction with the mosaic distribution of the i(12p) makes PKS often an underdiagnosed disorder. Since additional chromosome is usually absent in karyotypes obtained from cultured peripheral lymphocytes, clinical recognition with skin biopsy and fibroblast chromosome examination is of utmost importance.

86 FLOPPY INFANT SYNDROME DUE TO CONNECTIVE TISSUE DISORDER. CASE REPORT OF A PATIENT WITH KYPHOSCOLIOTIC EHLERS-DANLOS SYNDROME

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Introduction Ehlers-Danlos syndrome is a group of 13 hereditary connective tissue disorders due to defects in collagen formation, folding or interaction. Kyphoscoliotic EDS (kEDS) is characterized by severe congenital hypotonia, early-onset progressive kyphoscoliosis, joint hypermobility, hyperelastic skin and myopathy. The majority of patients have biallelic mutations in the PLOD1 gene, and others in the FKBP14 gene. The clinical phenotype is indistinguishable, except for hearing impairment, occurring in FKBP14-kEDS only. FKBP14-kEDS (OMIM 614557) is an ultra-rare disease with less than 30 patients described. We present our patient in order to raise awareness of connective tissue disorders in the differential diagnosis of floppy infant syndrome.

Case Presentation The patient was born after a normal pregnancy and delivery. Family history is unremarkable. Parents are unrelated. Joint hypermobility and weak cry were present at birth. Hearing screening revealed left-sided hearing impairment, confirmed by audiometry. Brain, heart, abdominal ultrasound and ophthalmic examination were normal. After the

discharge newborn thrived well but had a severe motor delay. He was referred to our institution at the age of 3 months with severe hypotonia, hypermobile joints, extremities in a frog-like position, redundant skin, no head control, bell-shaped thorax with pectus excavatum, mild thoracolumbar kyphosis, spina bifida occulta, umbilical hernia, undescended testicles, and talipes calcaneovalgus. Social contact was normal. Metabolic workup and gene analyses for spinal muscular atrophy, myotonic dystrophy type 1 and Prader-Willi syndrome gave normal results. Brain MRI was normal.

Electromyoneurography showed myopathy. Muscle biopsy revealed abnormal mitochondria and decreased activities of all respiratory chain complexes.

Mitochondriopathy was suspected and „mitochondrial-cocktail’ therapy was started. At two years of age, the patient was severely hypotonic, with myopathic face, hyperelastic joints and skin, easy bruising, thoracolumbar kyphoscoliosis, and normal mental development. He started to walk at the age of 3.5 years. At the age of 5 years, he developed severe osteoporosis and kyphoscoliosis progressed. Whole exome sequencing (WES) revealed homozygous mutation c.362dupC (p.Glu122fs) in the FKBP14 gene.

Conclusion Collagen myopathies should be in the differential diagnosis of floppy infant syndrome. Skin hyperextensibility and improvement of motor function with age may help to distinguish KEDS from collagen VI-related myopathies. Diagnosis can be confirmed by single gene or multigene panel testing. In a diagnostic dilemma, as in this case, in which some findings pointed to the diagnosis of mitochondrial disease, WES could be the best diagnostic approach. Accurate diagnosis ensures optimal patient management, complications insight, and appropriate genetic counselling.

87 KABUKI SYNDROME: REVIEW OF THE CLINICAL FEATURES AND DIAGNOSTIC FINDINGS IN FOUR CROATIAN PATIENTS

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Goal Kabuki syndrome (KS) is a rare malformation syndrome caused by mutations in KMT2D and KDM6A genes. Besides the cardinal manifestations, including distinctive facial appearance, mild-to-moderate intellectual disability, dermatoglyphic abnormalities such as persistence of fetal fingertip pads, skeletal anomalies and postnatal growth retardation, a wide spectrum of other anomalies is documented so far. We present clinical features and diagnostic findings in our four patients.

Methods During the 2016-2019 period, four of our patients were diagnosed with KS based on clinical observation and gene-targeted testing or comprehensive genomic testing (exome sequencing).

Results Three of our patients were males, one aged 17 and two aged 3 years, and one female aged 16 years at the time of diagnosis. Mutation of the KMT2D gene was identified in two patients, mutation KDM6A in one patient, while molecular analysis of one male patient is still in progress.

In addition to the five cardinal findings, one male patient had cleft palate, one had aortic coarctation with bicuspid aortic valve and one had multiple severe respiratory infections. Although susceptibility to autoimmune disorders is a known

feature in these patients, our female patient with KMT2D gene mutation was recognized as the first KS patient with systemic lupus erythematosus.

Conclusion KS is a rare disorder with highly variable clinical features making the diagnosis difficult. Consequently, a close collaboration between pediatric subspecialists, clinical geneticists and molecular biologists is essential in the terms of clinical recognition and genetic confirmation of this syndrome.

88 LOWE SYNDROME – OLD AND NEW EVIDENCE OF SECONDARY MITOCHONDRIAL DYSFUNCTION

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The oculocerebrorenal syndrome of Lowe (LS) is a rare, progressive, multisystemic X-linked disorder caused by mutations in OCRL gene. Patients classically present with ocular abnormalities including bilateral congenital cataracts and glaucoma, intellectual delay, severe generalized hypotonia with absent tendon reflexes, and proximal renal tubular dysfunction. Congenital bilateral cataracts and hypotonia are present at birth in almost all patients, while other classical symptoms develop gradually with variable severity. Consequently, differential diagnosis in infant period in these patients can be broad including other rare metabolic and neurologic disorders.

Herein we present a 4.5 year old boy with Lowe syndrome caused by novel mutation of OCRL gene (c.643C>T/p.Gln215*) initially diagnosed as having mitochondriopathy due to alteration of mitochondria on electron microscopic examination in different tissues and decreased values of mitochondrial energy metabolism measurements in muscle. No pathogenic mutations in mitochondrial DNA were found on whole exome sequencing.

This patient recall historical hypothesis of secondary mitochondrial dysfunction in Lowe syndrome, that may be caused/intensified some of disease symptoms.

89 FIVE-YEAR UPDATE FOR THE PHASE III VORETIGENE NEPARVOVEC STUDY IN BIALLELIC RPE65 MUTATION-ASSOCIATED INHERITED RETINAL DISEASE

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Goal To determine whether ambulatory navigation, light sensitivity, and visual field (VF) improvements 1 year after voretigene neparvec (VN) administration in patients with biallelic RPE65 mutation-associated inherited retinal dystrophy (IRD) are maintained at 5 years and review safety outcomes over the entire period.

Methods This is an open label, randomized, controlled Phase III trial performed at 2 sites in the United States. Patients were randomized to either original intervention (OI: bilateral subretinal VN at baseline; n=20) or delayed intervention (DI: VN after 1 year; n=9). The primary endpoint was bilateral