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Editors:
Bogdan Chiș, Simona Bucerzan, Paula Grigorescu Sido, Dan L. Dumitrașcu

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Foreword

It is our pleasure to introduce the abstract book of the Annual Meeting on Rare Diseases, Cluj-Napoca 22 February 2019.

This series of meetings evolved from the Gaucher Meetings initiated by Prof. Paula Grigorescu-Sido with the support of Sanofi many years ago. In time the scope of the meeting diversified, along with the spectrum of lecturers and attendants.

Rare diseases represent a major problem, because they remain frequently orphan: too few patients, too small therapeutic yield, too reduced interest to manage them, few but severely suffering people.

Things change in time and I am sure that in a few years tremendous progress will be registered in this domain. Our meeting is a small contribution and has mainly an educational purpose, addressing practitioners and doctors in training.

We wish you a good benefit from this meeting and from the abstracts published here.

The editors

Cardiac involvement in Fabry disease

Dan Radulescu, Liliana Radulescu, Bogdan Chis

Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Bogdan Chis
e-mail: chis.augustin@umfcluj.ro

Fabry disease is a genetic, X-linked lysosomal disorder, characterized by the absence of alpha-galactosidase A (α-GAL A) activity. Consequently, sphingolipids accumulate in the lisosomes and vascular endothelium of all tissues and organs. Main organs involved are the heart, brain, kidney, skin.

The main cardiac symptoms in Fabry disease are: dyspnea and signs of heart failure, chest pains, palpitations, syncope. In these patients, left ventricular hypertrophy, myocardial infarctions, arrhythmias and conduction abnormalities, valvular heart disease were reported. Left ventricular hypertrophy is present in about a third of the cases in women and half of the cases in men. The left ventricular hypertrophy and fibrosis is located mostly on the posterobasal wall. If left ventricular hypertrophy is present, there are associated cardiac symptoms, arrhythmias, valvular heart disease. The pattern of left ventricular hypertrophy is different from that in hypertension or infiltrative cardiomyopathies.

Valvular changes in Fabry disease are secondary to fibrosis and infiltration with lipids. These are represented by mitral valve thickening, mitral valve prolapse, aortic root dilatation with secondary regurge.

The tachy and bradyarrhythmias are due to lipid deposits in the conduction system. QT prologation and bundle branch or AV complete block may be present. Some patients necessitate cardiostimulation.

Angina and unstable coronary syndromes are secondary to endothelial dysfunction and severe left ventricular hypertrophy. Acute myocardial infarctions are reported in some patients.

The main cause of death in women is cardiac death, secondary to heart failure, unstable coronary syndromes, endocarditis, whereas in men the main cause is renal involvement.

In this presentation we describe two of our patients with Fabry disease, who presented with cardiac symptoms. We also discuss the treatment with alpha galactozidase and also if there is a degree of remission of left ventricular hypertrophy and cardiac symptoms, especially in young patients, during treatment.

Diagnosis, treatment and outcome in patients with Gaucher disease from Romania. Contributions to knowing the disease

Paula Grigorescu-Sido[1,2], Cristina Drugan[3], Anca Zimmerman[4], R. A. Popp[5], Camelia Al-Khzouz[1,2], Ioana Nascu[6], Cecilia Lazea[1,2], Calin Lazar[1,2], Simona Bucerzan[1,2]

1) Regional Genetics Center Cluj – Children's Emergency Hospital, Cluj-Napoca

2) Pediatric Department I - Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Biochemistry Department - Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Introduction. Gaucher disease is a autosomal recessive inherited monogenic disease caused by beta-glucocerebrosidase deficiency. Clinically, there are three types: type 1 (non-neuronopathic), type 2 (acute neuronopathic) and type 3 (chronic neuronopathic), in 92%, 1% and respectively 7% of patients. Specific diagnosis has been possible in Romania since 1997 and enzyme replacement therapy since 2002. The aim of the study is to present the epidemiologic, clinical and molecular data of the Romanian patients with Gaucher disease ant their evolution.

Patients and methods. 83 patients with Gaucher disease type 1 and 3 patients with Gaucher disease type 3; F/M = 1.38/1) were evaluated clinically and by measurement of

4) 1st Clinic of Internal Medicine, Yohannes Gutenberg University, Mainz, Germany

5) Department of Genetics, Molecular Sciences - Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

6) Emergency Unit - Children's Emergency Hospital, Cluj

Corresponding Author: Simona Bucerzan
e-mail: bucerzansimona@yahoo.com

haemoglobin, thrombocytes, hepatic and splenic volume, chitotriosidase, bone density (Z score) and severity index at diagnosis and every each 6-12 months. Seventy-four patients were treated with imiglucerase for a period of 1-15 years.

Results. Gaucher disease prevalence in our country, evaluated according to the number of patients diagnosed, is 1/233,000 vs. the potential prevalence of 1/100,000. Mean age at clinical onset was 15.4 years and 28.8 years at specific diagnosis. We found a high incidence of genotype N370S/L444P (38%) and of genotype N370S/? (32%), predictive for a severe phenotype vs 15.3% and 9.6% respectively in patients reported in International Gaucher Registry. Splenectomy was effectuated in 27.9% patients before the enzyme replacement therapy. Anaemia, thrombocytopenia, splenomegaly and bone disease were present in 52.9%, 37.7%, 100% and 91% of patients. The status of untreated patients was progressively worsening and six of the patients died. Enzyme replacement therapy led to normalization of haemoglobin, thrombocytes, hepatic volume and chitotriosidase after 0.5, 1.5, 2 and 3 years respectively. After 4 years of treatment, splenomegaly has been reduced from 14.4 of normal to 3.06 of normal. Clinical evolution of bone disease was favourable.

Conclusion. Gaucher disease is still undiagnosed in our country. Severe forms of disease are more prevalent. The patients have access to specific, enzyme and molecular diagnosis. Evolution under enzyme replacement therapy is very good.

Pulmonary hypertension and valvular involvement in Gaucher disease patients

Cecilia Lazea[1], Simona Bucerzan[2], Anca Zimmermann[3], Camelia Al-Khzouz[2], Mirela Crisan[3], Ioana Nascu[4], Radu Popp[5], Paula Grigorescu-Sido[2]

1) Pediatric Clinic I, Iuliu Hatieganu University of Medicine and Pharmacy, Emergency Children Hospital, Cluj-Napoca, Romania

2) Department of Genetic Diseases, Iuliu Hatieganu University of Medicine and Pharmacy, Emergency Children Hospital, Cluj-Napoca, Romania

3) Department of Endocrinology and Metabolic Diseases, University of Mainz, Mainz, Germany

4) Pediatric Clinic I, Emergency Children Hospital, Cluj-Napoca, Romania

5) Department of Medical Genetics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Cecilia Lazea
e-mail: cecilialazea@umfcluj.ro

Introduction. Gaucher disease is an autosomal recessive inhereted lysosomal storage disease characterized by long-term complications including pulmonary hypertension. The aim of the study was to assess the cardiac involvement in a group of Romanian GD patients with different genotypes.

Methods. We performed echocardiographic assessment in 71 patients with Gaucher disease (69 patients with Gaucher disease type 1 and 2 patients with Gaucher disease type 3). The following data were registered: age at diagnosis, age at start of enzyme replacement therapy (ERT), actual age, duration of ERT, genotype and splenic status. All patients were under ERT with human recom¬binant glucocerebrosidase.

Results. Among the 71 patients with GD participating in this study, nine patients presented calcification of the mitral or aortic valves. Mitral regurgitation of various grade was present in 30 patients (26 patients with mild mitral regurgitation, 3 patients with moderate MR and one patient with severe mitral regurgitation) and aortic regurgitation in 12 patients. Nine patients (12.67%) presented echocardiographic signs suggesting pulmonary hypertension. Five patients had splenectomy and 4 patients were without splenectomy. The mean SPAS in this group was 40.44 mmHg. Pulmonary hypertension was associated with age at starting therapy, years postsplenectomy and associated valvulopathy.

Conclusions. Pulmonary hypertension and valvular abnormalities represent the most frequent cardiac involvement in Gaucher disease.

Clinical, genetic characteristics and outcomes of Romanian patients with Gaucher disease diagnosed under the age of 18

Ioana Nascu[1,2], Paula Grigorescu-Sido[1]

1) Genetic Pathology Center - Children's Emergency Clinical Hospital, Cluj, Romania

2) Emergency Unit - Children Emergency Clinical Hospital, Cluj-Napoca, Romania

Introduction. Gaucher disease is a monogenic disease, with autosomal recessive transmission, caused by beta glucocerebrosidase deficiency. Three types are described with a prevalence of 92%; 1% and 7%, respectively. Diagnosis has become possible in Romania since 1997 and specific enzyme replacement therapy (ERT) since 2002.

Objectives. Presentation of clinical and molecular characteristics that allow specific diagnosis and outcome of patients with and without ERT.

Patients and methods. 25 patients (F / M = 1.12 / 1) clinically evaluated, haematological, radiological, imaging and molecular met the diagnostic criteria for Gaucher disease. Hemoglobin, platelet count, splenic and hepatic volume, chitotriosidase, bone mineral density and severity score were determined half-yearly.

Results. The prevalence of Gaucher disease in our country (1 / 300.000) is similar to that in Germany and Spain. Type I and type III were diagnosed in 17 and respectively 2 patients. The mean age was 6.4 years on clinical onset and 12.4 years on specific diagnosis. Thrombocytopenia, anemia, splenomegaly, hepatomegaly, bone disease were present at 20%; 60%; 30%; 20% and 20%, respectively. ERT resulted in normalization of hemoglobin, platelet count and chitotriosidase by 0.5; 1.5; 2.5 and 3 years of treatment respectively, net improvement of splenomegaly and improvement of bone disease. From January 2013, all patients are treated specifically.

Keywords: Gaucher disease, diagnosis, treatment

Neurological manifestations in Fabry disease

Adina Stan, Fior Dafin Muresanu

Neurosciences Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Adina Stan
e-mail: adinadora@yahoo.com

Fabry disease is an X-linked lysosomal disorder that leads to excessive deposition of glycosphingolipids in different organs, causing significant changes of skin, eye, kidney, heart, brain, and peripheral nervous system. The main neurological manifestations are ischemic strokes, peripheral neuropathies and autonomic dysfunctions. Fabry disease should be consider in all young patients (under 50 years old) presenting with signs and symptoms of a stroke, along with specific skin lesions, renal insufficiency, and cardiac disorders. After a first stroke, recurrent stroke is frequent; this is why the specific treatment should be initiated as soon as possible. The most frequent symptoms of peripheral nervous system involvement are burning pain in the hands and feet, particularly during fevers (acroparesthesias), exercise, heat, or cold intolerance. Enzyme replacement therapy stabilizes and may slow progression of Fabry disease, the sooner is initiate the treatment, the more is the benefit.

Fabry disease - still underdiagnosed

Bogdan Chis, Dan Dumitrascu

2nd Deptartment of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Bogdan Chis
e-mail: bogdan_a_chis@yahoo.com

Fabry disease is a X-linked lysosomal storage disease, with a very heterogeneous symptomatology. Sphingolipid globotriaosylceramide will accumulate in the lyosomes as the metabolism is interrupted, affecting the eye, skin, kidney, neurological and cardio-vascular systems. As the classical form is more severe, there are still mild forms with late onset. Although the males are particularly affected, with up to 1 in 40,000 estimated frequency, female cases are described, but no numbers are yet known. Depending on the source, the incidence varies from 1.8 percent in secondary screening in patients with hypertrophic cardiomyopathy to 1 in 117,000 when total cases were compared to total number of births. As the symptoms are very different from one patient to another, several conditions can be considered before the correct diagnostics. Most common differential diagnoses include rheumatic disorders or fibromyalgia (neuropathic pain), inflammatory bowel disease or peptic ulcers (in recurrent abdominal pain), fucosidosis (angiokeratomas), medications side effects (cornea verticillata), primary hypertension, atherosclerotic coronary disease, endocarditis or myocarditis (cardiac involvement), or complications due to diabetes mellitus (as the proteinuria with renal impairment). Several methods are used for diagnosis, with low rates of false positive tests (under 5%). Dried blood samples test are widely available. As the new treatments have good response, a better outcome is expected in early diagnosis.

In this presentation, we will describe the main causes of late diagnosis and what could be changed in patients' early management.

Clinical and paraclinical aspects in Pompe disease

Alina-Costina Luca, Andreea-Simona Holoc, Elena Braha

Pediatrics Cardiology Clinic, St Maria Hospital, Iasi, Romania

Corresponding Author: Alina Luca
e-mail: andreea_s_holoc@yahoo.com

Pompe disease (glycogen storage disease II) is an autosomal recessive disease, with multisystemic and progressive neuromuscular hypotony, caused by a mutation in the acid alpha-1,4-glucosidase gene (chromosome 17q23.5). The incidence of Pompe disease (PD) is 1/40,000; at adult form of Pompe disease has an incidence of 1/57,000 newborn per year. In classic from of PD with infantile onset the patient has severe hypotonie (20-30% cases), cardiac anomalies with congestive heart failure (50-92% cases), macroglossia, feeding difficulties (44-97% cases) and respiratory problems (27-78% cases). The non-classic variant of infantile-onset PD is manifestes in the first year of life as motor delays and progressive muscular hypotonie. Usually the cardiac involvement is mild. Late-onset of PD could be considered in patients with proximal muscular weekness and respiratory insufficiency, with no apparent cardiac involvement.

In conclusion, routine neurological and cardiac evaluation in Pompe disease by echocardiography is an essential part of the PD management, can follow the disease progression and response to treatment. The echocardiography should be performed by a pediatric cardiologist experienced in PD. A 24 hour ambulatory ECG should be perform as a diagnosis baseline of PD to highlight possible arrhythmias.

Structural abnormalities of the heart in patients with genetic diseases and facial dysmorphism

Mirela Crișan[1], Eva Kiss[2], Cecilia Lazea[1,2], Ana Curt[3], Paula Grigorescu-Sido[1]

1) Regional Genetics Center Cluj – Children's Emergency Hospital, Cluj-Napoca, Romania

2) Pediatric Department I – Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) "Axente Iancu" Pediatric Clinic I – Children's Emergency Hospital, Cluj-Napoca, Romania

Corresponding Author: Cecilia Lazea
e-mail: cecilialazea@umfcluj.ro

Introduction. Congenital structural abnormalities of the heart include a broad spectrum of clinical manifestations, prenatally conditioned, no matter the age of diagnosis or manifestation. One out of three patients is diagnosed with structural abnormalities of the heart, which can be minor/major or isolated/multiple. Genetic factors (malformations, dysplazia) and environmental factors (disruptions) are involved in the etiopathogenesis of heart defects.

Objectives. Assessment of the prevalence of the cardiovascular abnormalities, framing their etiopathogenesis, evaluation of the available diagnosis criteria and investigation of the therapeutic and prophylactic methods.

Material and methods. 982 children have been included in this study, ages between 2 months and 18 years old, hospitalized in the Genetic Pathlogy Centre, for different genetic diseases with facial dysmorphism. Clinical examination, doppler ultrasonocardiography, chest x-ray, and laboratory, cytogenetic, enzymatic and serology findings were used as work method.

Results. 378 patients out of the 982 patients were diagnosed with major structural abnormalities, of which 33.06% were represented by cardiac abnormalities (125 patients, 69 males and 56 females). The most frequent abnormalities were atrial septal defect (30.4%), ventricular septal defect (21.6%) and Fallot tetralogy (11.2%). In most of the cases, the diagnosis was based on echocardiographic criteria (59.2%) and most of our patients were diagnosed in their first year of life (59.2%). 79.2% of the patients presented only heart defects, whereas 26 of the patients also had other major structural abnormalities (20.8%). The patients with structural abnormalities of the heart usually had a chromosomial disorder (21 trisomy, most frequent) or a monogenic disease (osteochondrodysplasia, most frequent), but we also found that children with complex structural abnormalities, such as Goldenhar Gorlin syndrome or VACTERL association, children with contigous gene syndrome (velocardiofacial syndrome) and with typical phenotypic markers (Kartagener syndrome) presented a heart defect. Treatment consisted of prevention of bacterial endocarditis and of complications, management of cardiac failure and surgery correction of the defect (12%). Regarding complications, 28.8% of the patients developed vascular hypertension, 17.6% of them presented cardiac failure and 8.8% of them died.

Conclusion. Structural abnormalities of the heart in patients with genetic diseases and facial dysmorphism are serious pathologies, that can lead to the death of the patients unless a prompt diagnosis and serious treatment are made.

Integrated care – connecting medical care, social care and educational services

Zsuzsa Almási, Paula Neagu

NoRo Centre for Rare Diseases, Zalau, Romania

Integrated care for rare diseases means that patients with rare diseases can benefit from a holistic and person-centered approach by coordinating medical, social and educational services.

There has been an increasing interest in integrated care for rare diseases as it offers multiple benefits for patients and families.

Implementation of integrated care involves legislative changes, management capacity, collaboration, financial harmonization and involvement of patients and patient representatives.

One of the practical consequences of implementing the concept of integrated care is the establishment of care networks. In this way, a patient-centered care chain is created what leads to continuous, top-quality medical and social care, as close as possible to the home of the patient.

A good integration of the services reduces confusions, repetitions, delays, doubling or lack of services, the number of people lost in the system.

Providing integrated care is essential to improving health and social services outcomes. Improving service efficiency can lead to significant financial savings, better resource planning, more involvement of service users and free access to quality information.

NoRo Centre for Rare Diseases is functioning as an integrated service provider for rare diseases, as it offers medical services, therapeutic interventions, social care, and educational programs, and it belongs to a patient organization. As a healthcare provider is accredited as Center of Expertise in RD, and as part of the RO-NMCA ID network became a member of ERN ITHACA. NoRo Center is also part of RareResourceNet – the European Network of Resource Centres for Rare Diseases – which aims at accelerating the development and the implementation of holistic high quality care pathways for people living with a rare disease across Europe, to contribute to raise standards of care and support.

Diagnosis, treatment and outcome in patients with 21-hydroxylase and 11-β-hydroxylase deficiency (monocentric study, Cluj)

Simona Bucerzan[1,2], Paula Grigorescu-Sido[1,2], Camelia Al-Khzouz[1,2], Anca Zimmerman[3]

1) Regional Genetics Center Cluj – Children's Emergency Hospital, Cluj-Napoca, Romania

2) Pediatric Department I – Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Department of Endocrinology and Metabolic Diseases, 1st Clinic of Internal Medicine, Yohannes Gutenberg University, Mainz, Germany

Corresponding Author: Simona Bucerzan
e-mail: bucerzansimona@yahoo.com

Introduction. 21-hydroxylase deficiency (21-OH) - with two clinical forms: salt loss (SW) and simple virilizing (SV) - and 11-β-hydroxylase (11-β-OH) deficiency are rare monogenic diseases, (1/10 000-15 000 and 1/100 000), autozomal recesive, causing female pseudo-hermaphroditism (PHF), hypostature, hypertension, (11-β-hydroxylase deficiency) and salt loss syndrome (21-OH, SW), with possibly poor prognosis.

Objectives. Diagnostic, therapeutic and patient evaluation in our observation.

Methods. Clinical exam, specific hormonal examinations, molecular diagnosis, by sequencing the genes Cyp21A2 şi Cyp11B1.

Results. 21-hydroxylase deficiency (21-OH) was diagnosed in 54 patients (F/M: 37/17; SW /SV: 28/26) from 48 related families vs 1500 patients in the country. Comparing to other european countries, there is a higher frequency of I2G şi P30L mutations and a triple mutation, P30L+I2G+del8bp, still unreported. 11-β-hydroxylase (11-β-OH) deficiency was diagnosed in 6 patients (F/M: 3/4), from 4 unrelated families vs 200 patients in the country. P94L mutation is still unreported. Prenatal diagnosis is not yet available. Therapeutically: the treatment of acute metabolic imbalances has been improved in 21-OH deficiency SW type; the prednisone has been replaced with hydrocortisone and oral mineralocorticoid therapy was associated (reduced availability in the country!); the right choice of social sex; feminizing genitoplasty was performed in patients requiring it. Evolution is very good. One girl and one boy presented early hypergondadotropic puberty and 4 boys - remaining adrenal testicular tumors, with favorable evolution with hormone specific treatment. Through lectures, conferences, diploma thesis, doctorate, monograph, international grant, publication in specialized journals, we contributed to a better knowledge of the disease.

Conclusions. 21-hydroxylase deficiency and 11-β-hydroxylasedeficiency are still underdiagnosed diseases in Romania. Patients have access to specific diagnosis.Patients need to find Hydrocortisone (tablets) and Astonin or Florinef in the country.

Keywords: 21-hydroxylase deficiency, 11-β-hydroxylase

Rare forms of obesity in children

Camelia Al-Khzouz[1,2], Diana Miclea[2,3], Simona Bucerzan[1,2]

1) 1st Pediatric Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Regional Center of Medical Genetics Cluj, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania

3) Medical Genetics Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Camelia Al-Khzouz
e-mail: alkhzouz@yahoo.com

Introduction. Obesity is a chronic nutrition disorder characterized by excessive accumulation of fats in subcutaneous cellular tissue and/or other tissues as a result of imbalance between energy intake and expenditure (increased caloric intake/low energy consumption). Studies conducted so far have revealed that common obesity, the most significant form, is a multifactorial disease in which pathogenesis involves a number of genetic factors that transmit the predisposition and environmental factors that transform this predisposition into disease. In defining the phenotype of common obesity contribute several genes (polygenic transmission mechanism). These genes are involved in various functions such as food intake, energy consumption, lipid and carbohydrate metabolism, adipose tissue development (adipogenesis) or inflammatory process. Monogenic obesity accounts for only 3-7% of all cases of obesity. They are induced by mutations of the genes involved in the ontogenesis of the hypothalamic-pituitary region, as well as in the coding of cytokines and leptin/melanocortin spindle receptors responsible for appetite control and energy homeostasis of the human body. There are a small number of patients in whom obesity is associated with craniofacial dysmorphism, malformative syndrome and delay in psychomotor acquisition / intellectual disability - these are defined as syndromic obesity.

The aim of this study was to analyze the etiopathogenic structure of obesity in children.

The study included 246 overweight children (142 girls and 104 boys), with body mass index (BMI) above the 97th percentile, aged between 1 and 18 years, admitted during the last 5 years (2013-2017) to Medical Genetics the Department of the Children's Emergency Clinical Hospital from Cluj-Napoca.

The study method consisted in anamnesis; clinical check-up, anthropometric analysis (weight, waist, BMI; body composition analysis); biochemical tests: lipid profile, glycemia; hormonal assay: leptin, insulinemia, cortisol; neurological, psychological evaluation; standard karyotyping, FISH techniques, and gene polymorphism assays (SNP array) in selected cases.

Results. In the studied group predominated common obesity, polygenic (81%). In 49 cases, obesity was associated with craniofacial dysmorphism, malformative syndrome and/or delay in psychomotor/ intellectual disability (19%). Standard karyotyping and FISH techniques revealed Turner syndrome, trisomy 21, Prader Willi syndrome, Bardet Biedl syndrome in 5, 4, 2 respectively 2 cases. SNP array revealed in 8/36 cases pathogenic variants and likely pathogenic variants in 5 cases.

Conclusions. Despite all the progress made to date, only in limited number of cases was possible to identify the responsible gene and demonstrate the Mendelian transmission of obesity.

Keywords: obesity, polygenic, monogenic, syndromic

Idiopathic pulmonary fibrosis – *Rara avis* in pneumology

Ana Florica Chiș[1,2], Milena Adina Man[1,2], Monica Pop[1,2]

1) Department of Pneumology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) "Leon Daniello" Clinical Hospital of Pneumology, Cluj-Napoca, Romania

Idiopathic pulmonary fibrosis (IPF) represents a rare cause for interstitial lung diseases (ILD). It is characterized by progressive and irreversible decline in lung function. The disease newly occurs in about 10-12 per 100000 people each year. Although it is a pathology of the 6th and 7th decade, the disease might also occur earlier in life. The cause for developing IPF remains unknown, yet some risk factors are cited: smoking, viral

Corresponding Author: Ana Florica Chis
e-mail: anna_f_rebrean@yahoo.com

infections, and family history. Typically, the onset occurs gradually (often more than 6 months), with progressive exertional dyspnea and/or nonproductive cough. The diagnosis requires exclusion of any other cause for ILD, such as granulomatous diffuse parenchymal diseases (e.g sarcoidosis), exposure to drugs (e.g Amiodarone), eosinophilic pneumonia, Lymphangioleiomyomatosis, collagen-vascular diseases, and others. Typical findings on high resolution computer tomography scan and hystopathologic findings represent useful tools in diagnosis algorithm. Early diagnosis is mandatory. In terms of treatment, two drugs are now available, pirfenidone and nintedanib (approved with reimbursement also in Romania), with the main advantage of slowing down the progression of IPF in mild to moderate stages of the disease. In conclusion, IPF remains a devastating rare fibrotic lung disease, with a median survival of 2.8-4.2 years, that requires a multidisciplinary medical team, and with no proven effective treatment.

Congenital hypothyroidism through thyroid aplasia diagnosed at 6 months of age. Why?

Carmen Culcitchi[1], Camelia Al-Khzouz[2,3], Carmen Asavoaie[3]

1) Pediatric Clinic IV - Children's Emergency Hospital, Cluj, Romania

2) Regional Center of Medical Genetics Cluj, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania

3) Pediatric Clinic I - Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

4) Imaging Department - Children's Emergency Hospital, Cluj, Romania

Corresponding Author: Carmen Culcitchi
e-mail: carmenculcitchi@yahoo.com

We present the case of a male infant admitted to the Pediatrics Section IV Cluj at the age of six months for severe eating disorders and severe malnutrition secondary to a severe infectious disease occurring at 2 months ½ when the patient was hospitalized at the Satu-Mare Hospital for the investigation of prolonged neonatal jaundice.

The pneumonia that marked the onset of the disease had a fugitive development, complicating rapidly with sepsis, acute renal failure that required transfer to the Pediatric Nephrology Clinic Cluj.

Baby's condition continued to worsen requiring mechanical ventilation, then High Flow CPAP for 2 weeks.

It has been suspected clinically as a classic galactosemia, reason for which enteral nutrition with lactose-free milk formula was initiated, by nasogastric tube.

Laboratory tests performed to assess nutrition status at admission in the Pediatric Section IV revealed high TSH and T4 Free high levels. Following expert advice from Genetics Department of Pediatric Clinic I (lecturer Dr. Camelia Al-Khzouz), in conjunction with ultrasound (Dr. Carmen Asăvoaie), we established the diagnosis of congenital hypothyroidism by thyroid aplasia. After the initiation levotiroxine substitution therapy, the baby's progression (evolution ?) was slowly favorable, allowing the gradual resumption of oral feeding exclusively after approximately 3 months.

Genetic tests did not confirm the clinical suspicion of galactosemia.

The particularity of the case: the onset of a congenital hypothyroidism in the baby, namely that of „myxedema crisis", rare and life-threatening form of hypothyroidism, encountered in adulthood, becoming clinically manifest in stressful situations: infections, traumas, surgery, medications.

Acute intermittent porphyria

Bogdan Chis, Daniela Fodor

2nd Dept of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Bogdan Chis
e-mail: bogdan_a_chis@yahoo.com

Acute intermittent porphyria (Sweedish porphyria) is a rare autosomal dominant metabolic disorder, with female more likely to be affected, in wich hydroxymethylbilane synthase (porphobilinogen deaminase) deficiency will conduct to porphyrin precursors accumulation. Onset of acute atacks occur in second or third decade, can last from hours to several days, and if prolonged, hospitalisation is required. Intense, cramping abdominal pain is most common symptom, along with tachycardia. Other gastrointestinal symptoms include nausea, vomiting, diarrhea or constipation, and even painful ileus was described. Endocrine factors (as acute attacks rarely occur in very young and postmenopausal women), alcohol consumption or diet can trigger an acute attack. Dark urine (port wine) can also be present. Urinary porphobilinogen is essential for diagnosis. Pain treatment can require opioids, and barbiturics can be used to reduce seizures, if they occur. Long term treatment will require an interdisciplinary team. Psychological symptoms are not uncommon, as depression and anxiety disorder, even paranoia tend to occur in patients with frequent acute bouts.

In this presentation, we will discuss the pain management possibilities and the opioid treatment response, based on our experience.

Eosinophilic esophagitis

Elvis Popovici, Teodora Surdea Blaga, Dan Dumitrascu

2nd Dept of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Elvis Popovici
e-mail: ppvelvis@yahoo.com

Eosinophilic esophagitis, an immune-mediated disease of the esophagus, with a chronic evolution pattern, drew great attention upon it in the recent years. According to the last European guidelines on this disease, the updated results showed a rapidly evolving trend in the disease incidence and prevalence. The incidence of eosinophilic esophagitis was reported between 1 and 20 new cases per 100.000 inhabitants per year, and the prevalence varies between 13 and 49 cases per 100.000 inhabitants. Being an immune-mediated disease, there has been reported an association between eosinophilic esophagitis and rhinitis, asthma or eczema. Food allergens and aeroallergens are involved in the development of this disease. After exposure to the allergens, the esophagus becomes infiltrated with eosinophils. Together with mast cells, eosinophils determine tissue fibrosis and remodeling, secondary to the infiltration of the esophagus. A present debate is maintained whether eosinophilic esophagitis has an IgE pathway of development or an evolution via IgG4 pathway. The disease presents with non-specific clinical complaints which vary with age. Dysphagia, food impaction, heartburn, noncardiac chest pain are the most frequent complaints in adults. Although clinical and macroscopic changes seen at the upper endoscopy can raise the suspicion of an eosinophilic esophagitis, the diagnosis is made by microscopic examination of the esophageal biopsies, collected by upper endoscopy of the esophagus. The treatment concentrate upon 3 domains: diet, drugs and dilation. Elemental diet, allergy testing and 6-food elimination diet, based on the avoidance of the most allergenic foods, are the most cited dietary therapies being used. Treatment with PPIs induce symptoms remission and histology remission in half of the patients with this disease. Topical steroid treatments are effective in inducing histological and symptomatic remission. Systemic corticosteroids are not a routine recommendation due to their well-known adverse effects, being used in patients with severe symptoms. Endoscopic dilation of the esophagus has shown a short-term improvement of the symptoms. Taking into account that eosinophilic esophagitis can follow a fibrostenotic pattern in the evolution, early detection and treatment are mandatory. Better understanding of the subsequent processes could open the way to more targeted treatment options.

Achalasia

Teodora Surdea-Blaga, Bogdan Chis, Liliana David, Dan L. Dumitrascu

2nd Internal Medicine Department, Emergency Clinic Country Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Teodora Surdea-Blaga
e-mail: dora_blaga@yahoo.com

Achalasia is a major motility disorder characterized by a lack of relaxation of the lower esophageal sphincter (LES), and absence or spastic contractions of the esophageal body, due to a loss of neurons in myenteric plexus. It is a rare disorder (incidence 2.5/100000), and is more common in adults, around 30-50 years of age. Old age, Parkinson's disease, sarcoidosis, or tumors that invade LES can induce achalasia-like motility changes. The etiology is unknown. Viral infections, autoimmune disorders and genetic changes have been described. Dysphagia, thoracic pain, regurgitation, heartburn and weight loss are the most common symptoms in patients with achalasia. The reflux symptoms are resistant to PPI treatment, and can delay the diagnosis. Esophageal dilation can alleviate symptoms for a short period of time. Regurgitations persist, and nocturnal cough can develop.

The diagnosis of achalasia is suggested by dysphagia, often more severe to liquids, associated with reflux symptoms or thoracic pain. Upper gastrointestinal endoscopy shows a tight esophageal junction, and later on, esophageal dilation, alimentary residue or inflammatory mucosal changes. Barium swallow test can show a dilated esophagus withnon-propulsive, tertiary contractions, and a symmetric, regulated short stenosis of the LES – the "bird's beak" sign. Esophageal manometry confirms the diagnosis, based on the lack of LES relaxation and abnormal peristalsis. Using high resolution esophageal manometry with pressure topography (HREM-PT), the achalasia can be classified in type I (aperistalsis and incomplete LES relaxation), type II (pan-esophageal pressurization in at least 20% of swallows), and type III (at least 20% of swallows with a spastic aspect). In achalasia series, type II achalasia was the most common type, followed by type I and III. There are no drugs effective in achalasia. Patients should be referred to endoscopic (botulin injection, balloon dilation or per-oral endoscopic miotomy POEM) or surgical treatment (Heller cardiomiotomy). Endoscopic balloon dilation is rapid, quite efficient (success rate between 70-90%) and preferred in older patients or patients with comorbidities. POEM has better results than dilation and surgery in type I and type III achalasia. Surgical treatment is preferred in young patients, and is superior to endoscopic dilation.

Spinal muscular atrophy, standards of care. The experience of the Clinical Hospital for Children Cluj-Napoca

Mihaela Vințan[1], Monica Mager[1], Diana Orza[1], Mihaela Dubau[2], Remus Babici[2], Laura Bodea[2], Nicoleta Daraban[2], Alexandra Maris[2], Mihai Militaru[2], Loredana Oana[2], Diana Păcurar Vlonga[2], Sorin Man[3], Călin Lazăr[4], Cornel Aldea[5]

1) Department of Pediatric Neurology, Clinical Hospital for Children Cluj-Napoca, Romania

2) Department of Intensive Care, Clinical Hospital for Children Cluj-Napoca, Romania

3) 3rd Pediatric Clinic, Clinical Hospital for Children Cluj-Napoca, Romania

Spinal muscular atrophy (SMA) is a genetic disorder characterized by progressive weakness and atrophy of the skeletal muscles due to loss of motor neurons. It affects 1 per 8,000 to 10,000 people worldwide. There are recognised at least 5 types of disorders caused by the same mutation of genes SMN1 and SMN2 both providing instructions for encoding the survival motor neuron (SMN) protein which has an important role in maintenance of the motor neuron. The prognosis in bad with early death for SMA type 0, 1 and 2 and motor disability for types 3, 4 and 5. Considering these, standards of care have been set with international acceptance and promising treatments have been approved or are in trial procedure. Nursinersen was approved by the FDA in 2016 and by EMA in 2017 (who "recognised the serious nature of the disease and the urgent need for effective treatments") for treatment of patients with SMA, and it is a synthetic anti-sense oligonucleotide that increase

4) 1st Pediatric Clinic, Clinical Hospital for Children Cluj-Napoca, Romania

5) 2nd Pediatric Clinic, Clinical Hospital for Children Cluj-Napoca, Romania

Corresponding Author: Mihaela Vintan
e-mail: mihaela.vintan@umfcluj.ro

exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein, which is able to work normally, this replaces the missing protein and relieves the symptoms of the disease, route of administration is intrathecal. Since October 2018, 9 children with SMA started the treatment with Nursinersen in Clinical Hospital for Children Cluj-Napoca, type I (2 pts), type II (1 pts) and type III (6 pts). The injections were administered in the ICU under local anesthesia with lidocaine and prilocaine and sedation. Treatment was well tolerated by all children. Three of children finished the initiation (the first 4 doses), there were improvements in all children with gaining of at least 2 points (especially for type III patients) on special assessment scales (Hammersmith, CHOP Intend, RULM) even before the re-evaluation point that has to be (accordingto the protocol) after the 6th dose. We present clinical data of our patients group before and during Nursinersen treatment and their management in respect with the latest standards of care.

Establishing an etiological diagnosis in disorders of sex development

D. Miclea, C. Al-Khzouz, S. Bucerzan, A. Zimmermann, R. A. Popp, V. Cret, M. Farcas, M. Crisan, D. Stefan, P. Grigorescu-Sido

Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Emergency Hospital for Children, Cluj-Napoca, Romania

Corresponding Author: Simona Bucerzan
e-mail: bucerzansimona@yahoo.com

Disorders of sex development are a heterogeneous group of pathologies for which understanding of the pathogenetic mechanism is very important for the good management. Chicago Consensus Conference, in 2006, proposed a new nomenclature and a new classification, based on karyotype, so there are three major categories of disorders of sex development (DSD): 46,XXDSD; 46,XY DSD and sex chromosomes abnormalities DSD. Knowing the karyotype already directs to a certain pathogenetic pathway in thinking a case, but in a certain DSD category, there are multiple genetic factors that can lead to a quite similar phenotype and the clinical and hormonal phenotype it isn't enough to understand the pathology. Understanding more about the responsible genetic factors is possible today thanks to the next generation sequencing technologies that allow the evaluation of many genes involved in the development of DSD, sometimes the whole exome or whole genome. The knowledge of an involved gene allows the comprehension of the entire pathogenetic mechanism of a phenotype and thus allows valuable data for the long-term prognosis. In this presentation we will describe data about the genetic diagnosis in disorders of sex developments well as the limitations resulting from the use of new generation sequencing techniques for this type of diagnosis.

Genetic counselling in rare hereditary cancer

Andreea Cătană[1,2], Patriciu Achimaș Cadariu[1,2], Daniela Martin[2], Andrada Orodan[1], Radu Anghel Popp[1], Mariela Militaru[1]

1) Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Prof. Dr. Ion Chiricuta Oncology Institute, Cluj-Napoca, Romania

Corresponding Author: Andreea Catan
e-mail: catanaandreea@gmail.com

The last 2 decades of progress in molecular genetics have made possible a complex and elaborate array of genetic investigations tailored towards hereditary neoplasms. These are recommended and interpreted by the medical geneticists, aiding in informing the patient about potential individual hereditary predisposition towards neoplasms. Carriers of pathogenetic mutations predisposing towards cancer are introduced in a screening program, following current oncological guidelines, in order to detect any potential malignancies in a timely fashion, as well as in order to inform potential carriers in the patients' bloodline about the risk of carrying a pathogenetic mutation. Genetic counselling remains an important element in the multidisciplinary approach towards the oncological patient, offering solid benefits regarding diagnosis, prognosis and therapeutic management.

Genetics of malignant melanoma in children

Eleonora Dronca[1,2], Andreea Cătană[1,3], Mihai Militaru[4], Radu Anghel Popp[1], Mariela Sanda Militaru[1,2]

1) Department of Molecular Sciences, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Genetic Center, Cluj-Napoca, Romania

3) Ion Chiricuță Clinical Cancer Center, Cluj-Napoca, Romania

4) Department of Pediatrics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Eleonora Dronca
e-mail: eleonora.dronca@umfcluj.ro

Melanoma is the second most frequent type of cancer in adolescents and young adults. The incidence of this type of skin cancer increases approximately 10x with age, from the 1-4 years old to the age of 15-19 years old. In general, girls have a higher risk than boys, with a distribution mostly in the lower body, while in boys there is mostly an upper body distribution (head and neck).

The majority of cases are non-Hispanic whites (more than 80% of cases), followed by Hispanic individuals (5%) and Asian/Pacific Islanders (2%).

One of the most important risk factors in melanoma is UV light exposure that causes sporadic cases; in individuals that have other risk factors (e.g. positive family history, gene mutations, fair skin, nevi), UV exposure can cause early onset of the disease.

In more than 20% of cases, pediatric melanoma patients have non-modifiable risk factors (such as *xeroderma pigmentosum*, nevi, fair skin, positive family history, and genetic susceptibility). In approximately 1% of cases, there is a familial type of melanoma related to genes such as *CDKN2A*, *CDK4* or *MITF*.

Pediatric melanoma is classified as: conventional melanoma (CM), which is rarely diagnosed before puberty and which shows several similarities to adult melanoma, including evidence of UV-induced DNA damage and similar UV-induced mutations (such as the *BRAF* mutation); spitzoid melanoma (SM), which often lacks common adult melanoma genetic mutations (such as *BRAF* or *NRAS*); and congenital melanocytic nevus (CNM), of which approximately 5-10% develop into melanoma. Ocular melanoma and mucosal melanoma are rare forms of the disease and although uncommon, can also occur in children.

Each of these types has different risk factors and histology, and benefits from a different therapeutic protocol; therefore the histological, clinical and genetic differential diagnosis is very important.

In case of CM, there is a higher incidence of single nucleotide variations (SNVs) due to UV exposure (e.g. *TERT-p* gene mutations). CM and CNM can be differentiated based on the *BRAF* and *NRAS* mutations profile; in case of *BRAF* mutations in CM, an additional *PTEN* mutation is needed for the onset of the disease; while in CNM, *NRAS* mutations can trigger the onset without any additional gene mutations. Also, in melanoma, cells have various and complex chromosomal abnormalities (such as multiple additions and/or deletions); in SM, many genetic variations might be present including *BRAFV600E/BAP1*neg, *HRAS* mutant with increased copies of 11p, and homozygous 9p21 deletion with negative p16 expression. Kinase fusions of *ROS1*, *NTRK1*, *ALK*, *BRAF*, and *RET* can also be found in a mutually exclusive pattern.

Several genetic markers have been identified as potential prognostic indicators: *TERT-p* mutations, gains in 6p25 (*RREB1*), 11q13 (*CCND1*), and homozygous deletions of 9p21 (*CDKN2A*) are associated with a higher risk of aggressive clinical behavior in SM. Conversely, isolated 6q23 (*MYB*) loss and loss of 3p21 in *BAP1*-associated Spitz tumors are associated with a favorable clinical outcome.

Hypophosphatemic rickets – diagnostic and therapeutic aspects

Daniela Iacob[1], Andrei Corbu[2], Dan Cosma[2]

1) 3rd Pediatric Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Orthopedics - Traumatology and Pediatric Orthopedics Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Corresponding Author: Daniela Iacob
e-mail: daniela.iacob@umfcluj.ro

Introduction. Rickets is a condition in children that occurs due to a defect in bone mineralization leading to abnormalities of growth cartilage. It may occur due to deficiency of calcium, phosphorous or vitamin D. Rickets in childhood can produce growth retardation and bone deformity. Rickets can be classified in two major groups: calcipenic and phosphopenic. If calcipenic rickets due to vitamin D deficiency is still frequent, there are rare forms of phosphopenic rickets.

Material and method. We present the case of a 7 years old boy admitted for severe bowing of lower extremities.

Results. Physical exam indicated disproportionate short stature with short lower limbs and bone deformity with genu varum, similar with his mother. Biochemical evaluation indicated low serum phosphorus, normal calcium, normal parathormone, renal phosphate loss documented by decreased tubular maximum reabsorption of phosphate per glomerular filtration rate, normal 1,25 (OH)2 D3, elevated alkaline phosphatase. X-ray proved reduced bone density at knees, bilateral genu varum and coxa vara. Molecular genetic testing for PHEX mutation is pending. His mother has also low serum phosphorus. The diagnosis was X-linked hypophosphatemic rickets. Treatment was started with oral Phosphate titrated gradually to 2 g/day in 4 divided doses and Calcitriol in a daily dose of 0.5 μg/day, in 2 divided doses, targeting to maintain serum phosphorus in the low normal range. Then an external bilateral hemiepiphysiodesis was performed.

Conclusion. Growth retardation and bone deformity in our patient were due to X-linked hypophosphatemic rickets. A correct diagnosis is important for establishing the appropriate therapy.

Congenital lactic acidosis due to a mitochondrial defect. Case report

Ligia Blaga[1], Romana Vulturar[2], Gabriela Abrudan[3], Bogdana Todea[3], Adriana Ciubotariu[3], Marta Muresan[3]

1) Neonatal Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Cellular and Molecular Biology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Neonatal Department, Dominic Stanca Obstetric and Gynecology Hospital, Cluj-Napoca, Romania

Background. Congenital lactic acidosis is a rare disease that affect the enzymes that convert carbohydrates and fats in energy. As a result too much lactic acid is produced into the cells. Most of these enzymes are located in the mitochondria, so in most cases the disease is due to genetic mitochondrial enzyme deficiencies. It could be recessive or dominant or may occur spontaneously. The most severe cases have neonatal onset with tachypnea, hypotonia, vomiting and lethargy. It can be also a complication of other metabolic congenital diseases.

Material and method. We present the case of a preterm male newborn 36 weeks gestational age, from an unfollowed pregnancy, vaginal delivery, 2100 g birth weight, Apgar score 9. Affirmative inbreeding - parents are cousins. Mild respiratory distress with tachypnea, mild hypotonia and metabolic acidosis with high lactate level are present in the first hours of life. Vomiting occurs with the first milk meals. Sepsis work up and antibiotic therapy were started. Clinical condition has worsened. Hyperammonemia has been associated soon. A metabolic inborn disease was suspected. Enteral feeding was stopped, glucose and amino-acids infusion was administered; metabolic disorders work up were started. Aminoacidopathies that evolve with lactic acidosis and organic academia were excluded. Performing urinary MRI spectroscopy guides the diagnosis towards a severe mitochondrial defect. Unfavorable evolution, the baby died on the third day of life.

Discussion. Neonatal sepsis should be excluded from the start and antibiotic therapy should be initiated from the first few hours. There are no standard investigations for mitochondrial disease. The investigations are made in correlation with clinical presentation of the disease and the diagnosis is made by exclusion.

Conclusions. Only the identification of the specific gene mutation is specific and sensitive.

Keywords: congenital lactic acidosis, hyperammonemia, organic acidemia

Lynch Syndrome

Roxana Flavia Ilieș[1], Felicia Maria Bogdan[1], Gabriela Morar Bolba[2], Diana Militaru[1], Andreea Cătană[1,2], Eleonora Dronca[1]

1) Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Prof. Dr. Ion Chiricuta Oncology Institute, Cluj-Napoca, Romania

Corresponding Author: Jurcau Ramona
e-mail: ramona_mj@yahoo.com

Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant genetic condition, manifesting through a predisposition towards developing colon cancer. Its prevalence is variable in the general population. It is caused by germinal mutations in MLH1, MSH2, MSH6, PMS2 and EPCAM genes, which destabilise DNA and induce microsatellite instability, thus increasing neoplastic risk for colon, rectum, endometrial, gastric, ovarian, renal or intestinal cancers. HNPCC features a cumulative risk of 80% for the development of colorectal cancer by 70 years of age, and a 60% risk for endometrial cancer in women. Association with other neoplasms is rare.