

**Abstracts of the Conference:
The Day of the Rare Diseases**

**27 February 2020
Cluj-Napoca**

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Foreword

It is our pleasure to introduce to you the abstracts of our meeting on rare diseases.

Started as a symposium dedicated to lysosomal diseases, this meeting evolved in time, aiming and succeeding to bring together specialists (and representatives of the patients' associations). The new venue in Cluj-Napoca offered a perfect frame for lectures, discussions and networking.

Most speakers belonged to the Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca but we also had guests from the main medical centers in this country and again one foreign guest, this year from Bulgaria.

The main feature of the meeting is now its multidisciplinary. Rare diseases mean few patients and therefore we included in the program many case reports. On the other hand we also included the experience of centers with important patients records covering different medical fields.

This abstract book has the capacity to attract the interest of readers from many specialties. We hope you will find this abstract book both an enjoyable reading and a useful reference.

The Editors

The rare diseases in the era of big data

Dan L. Dumitrascu

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Background and aim. Rare diseases (also called orphan diseases in the FDA 1983 act) are rare indeed but expensive. Detecting and recording these conditions might benefit from the impressive progress in data processing.

Methods. A literature survey was undertaken in order to find out if the management of rare diseases is indeed influenced by the new facilities of big data storage and processing.

Results. The literature review found that in this field we still do not have evidence based data. However, technically it is very well possible to improve the recording and the follow-up of patients with rare diseases by using up-to-date IT methods. But for the moment, classical systems for storing and retrieving data on rare diseases are still useful.

Conclusions. The big data era opens a bright future to rare medical conditions, not only to diseases with high prevalence or endemic.

Fabry cardiomyopathy

Dan Radulescu, Elena Buzdugan, Laurentiu Stoicescu, Sorin Crisan, Alin Grosu, Liliana Maria Radulescu

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In the present paper we discuss the main symptoms in Fabry cardiomyopathy. We also present the left ventricular hypertrophy, associated valvulopathies, arrhythmias, coronary syndromes, heart failure, often present in this disease.

Left ventricular hypertrophy is evident 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 regurg. Cardiac magnetic resonance is very useful in documenting the left ventricular hypertrophy.

The tachy- and bradyarrhythmias are due to lipid deposits in the conduction system. QT prolongation and bundle branch or AV complete block may be present.

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

The cause of death may be secondary to heart failure, unstable coronary syndromes, endocarditis, renal involvement.

We also present a few cases of Fabry disease with cardiac involvement and discuss the therapy in these patients.

Early clinical manifestations in Fabry disease

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Fabry disease is a multisystemic, X-linked inherited disease induced by lysosomal alpha-galactosidase A deficiency, involved in the degradation of globotriaosylceramides which leads to excessive deposition of globotriaosylceramides in the vascular endothelium of several organs and in epithelial and smooth muscle cells (skin, eye, kidney, heart, brain, and peripheral nervous system). The clinical picture covers a wide spectrum ranging from mild cases in heterozygous females, to severe cases in classically affected hemizygous males. The most common early symptom of Fabry disease is the pain - chronic pain like burning and tingling paresthesia and acute episodic crises. Anhidrosis may occur causing heat and exercise intolerance. Other early signs include angiokeratoma, corneal changes, tinnitus, hearing loss, chronic fatigue, inappetence, recurrent abdominal pain, diarrhea, cardiac abnormalities, renal impairment and microvascular ischemic brain involvement.

The purpose of this study was to analyze the age when specific diagnosis was established in Romanian patients.

The working method consisted in analyzing the medical documentation of the patients at time of initiation of specific enzyme replacement therapy.

Results. The study included 38/59 specific diagnoses patients. The mean age of the patients included in the study was 44.08 ± 12.94 years. Interestingly 55% are women while 45% are men due to the fact that there is a higher percentage among men towards rejecting the treatment.

Conclusions. Fabry disease is a rare disease with childhood onset, but the early signs and symptoms are under-appreciated, and most often the diagnostic is delayed, 2-3 decades only when the damage of vital organs becomes manifest.

Gaucher disease – current status in Romania

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Gaucher disease is an autosomal recessive lysosomal storage disease in which sphingolipids (glucocerebrosides) accumulate in the organs. Liver and spleen enlargement, low platelets counts, bone crisis, anemia, fatigue are the most commonly found in Gaucher patients. Its incidence is about 1:50,000. There are three types (type 1 non-neuropathic form is the most common, with better outcome, while type 2 is more severe, with early onset and neurological involvement). Treatment options are continually studied. The first options was enzyme replacement therapy (ERT-intravenous administration). Substrate reduction therapy (SRT- an oral medication) is now available for certain patients (depending on the CYP2D6 metabolizer status).

In Romania, there are at the moment 76 treated patients (out of 78 known), with one type 3 disease and the rest suffering of type 1 disease. 6 patients are under 18 years old. 53 patients receive ERT, while 23 receive SRT. None of them (disregarding the treatment form) suffer of severe or symptomatic thrombocytopenia. Severe liver or spleen enlargement is rarely found, with good response to dose increase. Fatigue is the

most common symptom found, but it tends to ameliorate under the treatment, along with quality of life (based on SF 36 questionnaire). No neurological severe symptoms are found.

Gaucher disease remains underdiagnosed in Romanian population, considering 200 patients predicted on general incidence in Eastern Europe. General screening of patients with unexplained liver or spleen enlargement, low platelets or anemia, should be considered.

Rare causes of stroke - Fabry disease

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About 20-25% of strokes are cryptogenic or of unknown etiology, and this percentage is higher in young patients. Rare causes may be suspected in a stroke patient with unusual clinical or radiological features and unexpected recurrence. These rare causes involve vasculitic, prothrombotic, genetic, drug-related, iatrogenic, or other mechanisms. Hereditary causes include Fabry disease, CADASIL, MELAS diseases. Rare diseases have signs and symptoms common with other pathologies, and the diagnostic process can take years, during which the impact on the functional outcome becomes irreversible. Fabry disease is a multisystemic, progressive, potentially lethal, genetically transmitted disease that affects both men and women. It 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 considered 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. Early recognition and treatment of this condition significantly improves the prognosis of patients with Fabry disease.

Dual cancer in a patient with type 1 Gaucher disease: a case report

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We present the case of a patient diagnosed in 2006, at the age of 63 years, with Gaucher disease type 1, when he presented progressive fatigue, upper abdominal discomfort, pallor, as well as minor bone pain of the lumbar spine. On physical examination massive hepatosplenomegaly and multiple ecchymosis were found. The laboratory tests revealed anemia (Hb:9,7g/dl), thrombocytopenia (45.000/mm³), and elevated serum ferritin. The patient underwent bone marrow biopsy, which revealed the presence of Gaucher cells. The definitive diagnosis was based on enzyme level and genetic testing (genotype N370S/R463C). In 2007, during follow-up, the patient was diagnosed with renal cell carcinoma and nephrectomy and necessity splenectomy were performed. In 2012 enzyme substitution therapy with Imiglucerasum was initiated, the overall evolution was favorable. Seven years after the initiation of therapy the patient overall condition improved significantly. However, in 2019 a 5.5/3.8 cm hyperechoic mass was visualized by ultrasound in the VIIIth liver segment. CEUS and computer tomography were inconclusive for a definite diagnosis and core biopsy was performed, which revealed a poorly differentiated hepatocellular carcinoma G3. Considering the good condition of the patient, a non-anatomical resection

of liver segments VII and VIII with partial resection of inferior vena cava was performed, followed by full recovery. The particularities of this case are: diagnosis at an advanced age, good response to treatment despite the age, occurrence of two independent cancers during follow-up. We can conclude that a close follow-up of patients with Gaucher disease is needed because of the increased risk of malignancy.

Collaboration between professionals and patients in the field of rare diseases in Romania

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2) NoRo Center, Zalau, Romania

Romanian Prader Willi Association and National Alliance for Rare Diseases are working together with professional organizations in order to improve the care services for patients with rare diseases to address their needs;

NoRo Center is a result of collaboration between professionals and patients and offers a model of good practice of integrated care.

It was opened in 2011 through a Norwegian grant and a mentoring program with Frambu Resource Center for Rare Diseases in Norway.

NoRo interdisciplinary team is facilitating activities of support group, psychological counseling, evaluation and therapeutic education for parents and access to therapies for children and young people with rare diseases.

Results: 140 – 150 patients and personal assistants/ year in groups, 60 children in Day Care Center, more than 400 requests solved on Help Line/year, 3-4 workshops and trainings organized/ year and around 200 people / year attending conferences;

In 2016 we established Ro-NMCA-ID (Network Multiple Congenital Abnormalities with Intellectual Disability) and became members of ERN ITHACA, in 2017 we were accredited as a Center of Expertise for rare diseases and autistic spectrum disorders.

NoRo has initiated the European network of resource center for rare diseases RareResourceNet.

Conclusions. Together, everybody achieves more (TEAM): Organizing supportive networks, developing resource centers where patients and professionals are a TEAM, improved the access to care for patients with rare diseases in Romania.

hATTR – Familial Amyloid Polyneuropathy in Bulgaria, an overview

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Background. Hereditary transthyretin amyloidosis (hATTR) is not a well-recognized disease in Bulgaria. The study of the disease only began after its first clinical diagnosis in 2008 and subsequent genetic diagnosis in 2010.

Methods. DNA sequencing of TTR gene.

Results. Between 1 April 2008 and 1 July 2019, five different transthyretin

gene mutations were found: Glu89Gln, Ser77Phe, Val30Met, Gly47Glu, Ser52Pro. The data collected in a registry consisted of more than 100 patients with and more than 100 asymptomatic carriers, allowing preliminary epidemiological data of the disease, its incidence and prevalence. The Glu89Gln, Ser77Phe and Val30Met mutations have distributions with a geographic focuses, while Gly47Glu is limited to people of Romani descent. The distributions of Glu89Gln and Val30Met do not follow the current political borders with neighboring countries. The high incidence and prevalence rates of Glu89Gln are greater than 1 in 10,000, defining the southwestern part of the country as endemic for this mutation.

Conclusion. Our preliminary data indicate that there have been many diagnosed cases of hATTR in Bulgaria in the last ten years. We anticipate that there is a significant number of as yet unidentified patients and carriers. Discovering de novo patients is an ongoing process. New patients from newly identified families or relatives of patients from known families appear constantly. This indicating that hATTR may not be as rare within the Bulgarian population as was initially believed.

Arrhythmogenic right ventricular dysplasia in children

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Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiac disease characterized by fibro-fatty replacement of the right ventricular myocardium, paroxysmal ventricular arrhythmias and sudden cardiac death. Left ventricle can be also involved. The inheritance is autosomal dominant or recessive. The diagnosis is based on major and minor clinical, electrical and imaging criteria. In children, the diagnosis is difficult to be established because of the paucity of the clinical and imaging changes. We report two patients diagnosed with ARVD and the literature review regarding the diagnosis criteria.

Association between hepatic arterio-venous malformation and ascites. Diagnostic pitfalls

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Congenital arteriovenous malformations (AVM) are vascular abnormalities of the liver with abnormal vascular connections between the portal vein, hepatic artery and hepatic vein by which the capillary bed is shunting. As a result a shunt from the high-pressure arterial system to the low-pressure venous system develop. Usually one lobe is

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interested. The vascular malformations appear during the morphological development of the vascular system and they are present at birth. Their real incidence is unknown. Clinically, they may start with severe symptoms or may be asymptomatic. They can be isolated or syndromic. The diagnosis warrants complex imaging evaluations: ultrasound, MRI, CT scans, angio-CT.

Material and method. In this paper we approach some aspects and pitfalls of postnatal diagnosis of hepatic AVM. We present a case of arteriovenous fistula with hepatic location with onset as fetal ascites. Complex imaging evaluations were necessary: ultrasound exam, MRI, angio-CT scans. The stabilization of the patient included correction of the hepatic, cardiac and renal failure and of the associated coagulation disorders. Liver transplantation has been done in a specialized center of pediatric hepatobiliary surgery. The impairment of hepatic circulation was due to a rare hepatic structural abnormality.

Conclusions. Solving these cases requires the existence of a multidisciplinary team: obstetrician, neonatologist, interventional radiologist for establishing the diagnosis, but also high-specialized surgery services.

Peripartum cardiomyopathy in a young female patient

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Peripartum cardiomyopathy (PPCM) is a rare form of dilated cardiomyopathy (DCM), with an incidence of 1:2500-4000 live births. It is defined as heart failure (HF) secondary to left ventricular systolic dysfunction, which occurs towards the end of pregnancy or in the 5 months following delivery, in the absence of another identifiable cause. This case describes a 35-year-old female patient, in the early postpartum period, which was admitted to the Cardiology Department for signs and symptoms of HF following an episode of pneumonia. Echocardiography revealed a dilated cardiomyopathy, with a left ventricular ejection fraction of 20%. In order to differentiate PPCM from post-myocarditis DCM, cardiac MRI was performed, showing subepicardial LGE of the lateral left ventricular wall in the absence of edema. These findings were suggestive for PPCM. Management of this patient included standard HF treatment, associated with Bromocriptin. One-month follow-up showed an improvement of LVEF (30%). Finding the etiology of DCM can be very challenging. We emphasize the role of imaging in the diagnosis and management of these patients. Although PPCM is a rare condition, it should be considered in young female patients with symptoms of HF following delivery. Moreover, if treated, it is associated with a higher rate of recovery than other forms of HF with reduced systolic function.

Osteogenesis imperfecta. The experience of the Medical Genetics Department of Cluj

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Introduction. Osteogenesis imperfecta, a genetic disease of bone formation, with autosomal recessive or dominant inheritance, is characterized by bone fragility and reduced bone mass due to mutations in genes coding for type I collagen. The varying

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clinical severity is due to an imperfect genotype-phenotype correlation. Because the treatment with bisphosphonates (antiresorptive agents) was recently introduced, the authors have proposed to evaluate the effects of pamidronate these patients.

Patients and method. A total of 22 patients (9 girls and 13 boys, ages: 1 month-18 years) are diagnosed with osteogenesis imperfecta and registered in the Center of Genetic Disease of the First Pediatric Clinic Cluj. Out of these, 13 were treated with bisphosphonates and included in the present study. Evaluation of these patients was based on clinical, biochemical and radiological assessment as well as osteodensitometry, occupational and Z scores.

Results. Treatment with bisphosphonates (Aredia, Pamidronate Torrex) in 13 patients was administered in 2 - 14 cycles, at a dose of 0.25 - 1 mg/kg/day IV, 3 consecutive days at a 4-month interval. The drug was well tolerated, with the exception of fever recorded in the first cycle of treatment in 4 patients. Biochemical parameters of phospho-calcic metabolism remained within normal limits, except for reduced alkaline phosphatase values in a girl who associated hypophosphatasia tarda. Pending treatment, ostalgia resolved in all patients, the occurrence of fractures was limited to three patients, and the occupational and Z scores showed improvement.

Conclusions. Bisphosphonate treatment in osteogenesis imperfecta provides significant clinical improvement.

Orthopedic surgical challenges in Osteogenesis imperfecta

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Introduction. Osteogenesis imperfecta (OI) is a bone dysplasia characterized by bone fragility and pathological fractures caused by low bone mass and modified bone structure. Osteogenesis imperfecta is a rare genetic disease, with autosomal dominant and autosomal recessive forms, 90% arising from mutations in genes encoding type-I collagen (COL1A1 and COL1A2). OI patients have an increased risk of fracture throughout their lifetimes. Fractures heal normal initially, but the bone does not remodel, thus leading to serious complications, including progressive bowing. The aim of this study was to analyze the surgical treatment challenges and outcomes of OI patients with fractures.

Material and methods. A monocentric and observational retrospective study was conducted on 7 patients (3 males and 4 females) diagnosed with Osteogenesis Imperfecta, that were admitted in the Orthopedics and Traumatology Clinic of Cluj-Napoca, between January 2012 and January 2020. Mean age was 51 yr. (32-81). All patients were hospitalized for lower limb fractures.

Results. A number of 5 patients were treated operatively, using plates, screws or intramedullary nails. Increased length of stay was observed (15.8 days). Most of the patients had complications, such as delayed union (4 patients), vicious consolidation (6 patients) and subsequent fractures (3 patients).

Conclusions. Osteogenesis Imperfecta is a source of considerable morbidity. Treating fragility fractures on patients with this condition is technically demanding for the orthopedic surgeon, with an increased rate of complications.

The wide spectrum of rare gynecological cancers: a focus on non-epithelial ovarian tumors

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Approximately 18.5 million women annually are affected by a gynecological cancer. While all types of ovarian cancer are uncommon, certain subtypes are extremely rare. About 10% to 15% of ovarian tumors are considered rare. Rare gynecologic malignancies are defined with an incidence $<6/100,000/\text{year}$, however they represent over 50% of gynecologic cancers and involve more than 30 histological subtypes. Some of the most important challenges are to identify the right diagnosis, to define the prognosis, to define the best “standard” of care that includes the choice between radical surgery versus fertility sparing surgery, the selection of patients for adjuvant therapies and also to define the best option in relapse, and to develop international collaboration through professional organizations such as ESMO, ESGO, Euracan and GCIG. The EU is actively involved in creating a unique network between key stakeholders through the GYNOCARE project that covers five distinct domains, from concept to cure: basic research on rare gynecological cancer, biobanking, industrial dimension, legal and regulatory requirements for international trials and other research collaborative efforts, and high-quality, international, and innovative clinical trials.

Rare hereditary cancers. Genetic counseling in Li-Fraumeni syndrome

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Li-Fraumeni syndrome is a rare hereditary genetic disorder that increases the risk of developing several types of cancer, especially in young adults and children. Individuals with pathogenic mutations in the TP53 gene have an increased risk of developing breast cancer, sarcomas or other soft tissue malignancies as well as brain, adrenocortical, renal tumors and leukemia. The risk of developing a malignant tumor in carriers is about 70% for men and almost 100% for women up to 70 years, as in children the risk is estimated around 12-20%. The condition is autosomal dominant, but about 20% of patients may develop de novo mutations, which makes therapeutic and prophylactic oncological management difficult. Genetic counseling in Li-Fraumeni syndrome presents a series of particularities with significant personal, family and ethical implications for both the patient and his family. For a better understanding of the ones presented above we will discuss in this context 3 cases of Li-Fraumeni syndrome.

Cerebral lesions in Bouneville's tuberous sclerosis

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Introduction. Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with multisystemic involvement resulting from mutations in the TSC1 or TSC2 genes. As a result there appear a number of lesions involving the skin, nervous system, heart, kidney, and also other organs. Neurological involvement is taken into account once the patient has seizures or shows mental retard.

Materials and methods. Descriptive statistics of the number of patients Also were recorded the number of patients with everolimus treatment, and the types of cerebral lesions encountered.

Results. Of the 32 patients followed up, 22 presented brain lesions. Eight patients suffered from both epilepsy and mental retardation, one had only mental retard, 9 only epilepsy and 5 had systemic involvement with brain lesions but without epilepsy or mental retard. 95.4% of the patients (n=21) had epilepsy at debut, and 4.5% of the patients (n=1) had a later onset form of epilepsy. 63,63% received everolimus treatment. In 86% of the patients (n=19) the brain lesions observed were cortical/subcortical tubers, followed by subependymary nodules/hamartomas (54% - n=12) with a lesser dominance were associated SEGA (22.7% n=5, brain atrophy (4.5% n=1), optic nerve astrocytoma (4.5% n=1), intracranial hypertension (9% n=2), hydrocephalus (9% n=2), leucoaraiosis (9% n=2) and cavernomatosis (4.5% n=1).

Discussion. Although tuberous sclerosis is characterized by early-life neurological manifestations, primarily epilepsy, there is also a large proportion of these who do not have the typical neurologic impairment. These patients present other organ lesions, may present brain lesions and may be neurologically silent. Also, many of these patients did not present with growing mental retardation.

Juvenile-onset polyarteritis nodosa: an adult series

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Introduction. Polyarteritis nodosa (PAN) is a middle-size vessel necrotizing vasculitis manifesting with *livedo reticularis* and hemorrhagic and/or ischemic events. Some juvenile-onset and familial cases have recently been associated with adenosine deaminase 2 deficiency, due to *ADA2* or *CECRI* mutations.

Objective. We retrospectively assessed the adult patients with juvenile-onset PAN presented in our center over the last 5 years (Jan 2015-Jan 2020).

Material and method. The medical records of the patients were studied. The patients identified were called for further detailed assessment, testing and follow-up.

Results. A total of 7 patients were found (4 M, 3 F), age 30.2 yrs (18-41 yrs), age at vasculitis onset 10.2 yrs (3-16 yrs). Clinical involvement included: recurrent fever (4 patients), limited cutaneous PAN (3 patients, 2 related), oral ulcers (1 patient), cerebral

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involvement with stroke (2 patients- 1 also with retinal vasculitis), hepatosplenomegaly (3 patients- 1 with portal hypertension), recurrent hemophagocytosis (1 patient). Common variable immune deficiency was found in 2 and selective immunoglobulin deficiency in 3 patients respectively. Genetic tests were performed in 2 patients (1 heterozygous for a pathogenic loss-of-function *ADA2* variant, 1 compound heterozygous for 2 *ADA2* variants of uncertain significance). The therapies employed were glucocorticoids, azathioprine, cyclosporine, cyclophosphamide, hydroxychloroquine and immunoglobulins, with suboptimal response in 3 patients. Anti-TNFs and thalidomide were not available.

Conclusion. In juvenile-onset PAN genetic testing should be used for adjusted therapies and genetic counseling. A local registry and availability of effective treatments could improve the prognosis.

Primary immunodeficiency disorders associated with noninfectious hepatitis

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Chronic-recurrent infections with different pathogens are a hallmark of several primary immunodeficiency disorder, caused by genetic defects. Heterozygous STAT1 gain-of-function (GOF) mutations have increasingly been identified worldwide and underlies a variety of infectious and autoimmune disease.

We report the case of a 9-year-old girl who presented for recurrent oropharyngeal candidiasis, lower recurrent respiratory tract infections, failure to thrive, recurrent small abscess of the finger pulp and diarrhea. The onset of symptomatology was at the age of 11 months. Physical examination revealed failure to thrive, fingers clubbing (Hippocratic fingers), oropharyngeal candidiasis, small abscess of a hair follicle gland at the base of eyelash and of the finger pulp, bronchitis; no hepatosplenomegaly. Thoracic CT revealed *bronchiectasis*. Abdominal hydrosonography showed inflammatory aspect of the ascending colon. Laboratory findings: *erythrocyte sedimentation rate*, *C-reactive protein*, procalcitonin at normal values; very severe aminotransferase elevation; antinuclear antibodies constantly positive; the sputum culture revealed the chronic presence of *Staphylococcus aureus*, *Haemophilus influenzae*. We suspected primary immunodeficiency disorders. Genetic analysis revealed c.1154C>T (T385M) STAT 1 mutation (de novo) which was described quite recently. Treatment was symptomatic (antibiotic, and antifungal) at the time of recurrence of infections and we started corticosteroid therapies with a good clinical response, without serious infectious complications.

IgG4 related disease - a rare entity with multiple shapes

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Introduction. Hyper IgG4 syndrome is a rare autoimmune fibro-inflammatory condition, which can involve essentially any organ. The most common clinical presentation is the enlargement of one or multiple organs caused by masses of IgG4 infiltrates, that produce plasma cells, lymphocytes and fibrosis. In most of the cases the differential diagnosis with malignancies is necessary. Ocular involvement is identified in a small amount of cases, leading to usually bilateral exophtalmia.

Case presentation. A 32-year old male patient, diagnosed with diamine oxidase deficiency and vitiligo was admitted to our clinic with severe bilateral exophtalmia for the past 3 years, unaccompanied by pain and normal visual acuity. Previous investigations excluded hypothyroidism or any other form of cancer and the response to low doses of glucocorticoids was unsatisfactory.

The patient was investigated ecographically, which revealed enlarged, non-homogenous lacrimal glands, with no involvement of the salivary glands and local lymph nodes, and a normal thyroid gland. The orbital angio-RM showed an orbital idiopathic inflammatory process involving both orbits and the blood test results were inconclusive. The clinical presentation, the negative cancer screening and the normal biological results conducted to the suspicion of an autoimmune disease, the IgG4 related disease being the pathology that causes orbitopathy the most frequent. Serum IgG4 was >135 mg/dl.

Despite the patient's medical history, corticosteroid treatment was initiated, as it is considered the first line of therapy. As the patient was corticoreistant, Rituximab was the next best choice of therapy. The patient followed two doses of Rituximab, concomitant with GCs.

Conclusion. The IgG4 related disease is an under recognized condition, which affects males more than females. It has a variety of clinical implications and there is no reliable biomarker for its diagnosis. Careful investigation and monitoring of the patient are the only certain path for a correct diagnosis.

A rare case of Schnitzler's syndrome without a monoclonal gammopathy

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Introduction. Schnitzler's Syndrome (SS) is a rare, late-onset acquired auto-inflammatory disease. The main feature of the disease is the association of a chronic urticarial rash and a monoclonal gammopathy. The major complications of the disease are systemic AA amyloidosis and lymphoproliferative disorders (mainly Waldenstrom's macroglobulinemia and lymphoma).

The case description. A 43-years-old woman presented with 10 years history of chronic non-pruritic urticarial rash involving the trunk and extremities, associated with intermittent fever, arthralgias and axillary lymphadenopathy. The rash resolved within

12-24 hours without any cutaneous sequelae and was not responsive to antihistamine medication, Cyclosporine, Colchicine and Prednisone in doses of less than 15 mg/day. Laboratory tests revealed high ESR and CRP, leukocytosis with neutrophilia. Extensive immunological work-up was negative: ANA, anti-dsDNA, anti-CCP, RF, anti-Ro, anti-La, cryoglobulins, normal C3 and C4. Serum protein immunoelectrophoresis did not show monoclonal IgM. Lesional skin biopsy showed perivascular infiltrate of neutrophils, lymphocytes and eosinophils with reduced leukocytoclastic vasculitis. Immune deposits of IgM along the basement membrane was found by direct immunofluorescence test. In these settings a diagnosis of SS without monoclonal gammopathy was made.

Discussion. Although the diagnosis of SS requires the presence of monoclonal gammopathy as a key criterion, several case reports show that in atypical form the gammopathy may be absent in the early stages and may appear later as the disease progresses.

Conclusion. SS should be considered as a differential diagnosis in an adult patient with chronic urticarial rash when symptoms and signs of systemic inflammation are present.

Diagnostic difficulties of Wilson's disease in children

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Wilson's disease (WD) is a rare disorder of copper metabolism with an autosomal recessive transmission. In children, the most frequent clinical presentation is the liver disease, but in adolescents acute liver failure (ALF) with non-immune hemolytic anemia could be the first presentation of the WD. In adolescence and young adulthood, the main form could be neurologic and/or psychiatric.

Early diagnosis of WD requests a high level of suspicion, being based on a combination of clinical signs, biochemical tests, histology, and genetics. Kayser-Fleisher ring is not as frequent in children as it is in adults. 24-hour urinary copper excretion in children could be in the normal range and the d-penicillamine challenge test should be performed to increase the likelihood of diagnosis. In our country, the measurement of the copper content of the liver tissue is not possible. There are non-invasive methods used in WD patients as transient elastography was tried for the follow-up of the evolution of the disease and fibrosis. In the last years, the genetic tests are easier to use and more affordable as prices and this could help for WD diagnosis. There are more than 500 mutations and polymorphisms of ATP7B gene responsible for WD. The diagnosis, the prognosis and the need for liver transplantation in ALF presentation could be assessed using dedicated scores.

The evolution of the WD in children could be improved by early diagnosis and treatment, but in some cases, the only option for long-term survival could be the liver transplantation.

Old and new in Wilson's disease

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Wilson's Disease (WD) is a rare autosomal dominant inherited metabolic disorder, consequence of mutations in ATP7B gene. It is characterized by polymorphous clinical manifestations: hepatic, neurological, ocular, cardiac, renal and osteoarticular.

Although there are earlier mentions, its first complete description dates from 1912, in a publication of Samuel Alexander Kinnier Wilson. The knowledge on WD has been built all along the XXth century and the beginning of the XXIst. Certain scholars, such as John Walshe or Peter Ferenci, have contributed substantially to the actual understanding of the disease, dedicating their professional lives to this purpose.

The disease occurs in 12-25 persons/1 million, but consanguinity may lead to a surprisingly high prevalence, mainly in isolated areas.

The abnormal accumulation of Copper in the hepatocytes leads to alterations of the oxidation mechanisms and finally to cell death. Release of free Copper in the blood stream results in secondary affectation of the other above-mentioned organs. The phenotypical expression of the genetic mutations is modulated by epigenetic factors, leading to clinical diversity even in siblings.

The liver's suffering spans from asymptomatic laboratory changes to fulminant liver failure. The liver biopsy confers diagnostic certainty.

In addition to the classical neuropsychiatric and ocular findings, the novel technological advances have opened interesting paths for research and diagnosis: quantitative MRI, neuro-ophthalmology, retinal Optical Coherence Tomography.

As many other rare diseases, WD suffers from embarrassing diagnostic mistakes and delays. New screening methods and algorithms are studied to overcome this setbacks, taking into account the geographical differences in financial possibilities.

Duchenne muscular dystrophy – diagnosis and treatment options

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Background. Duchenne muscular dystrophy is the most common muscular dystrophy, with an incidence of one in 5000 boys. It is an X-linked recessive genetic disorder caused by defects in the dystrophin gene. Abnormality in the dystrophin protein causes progressive muscle damage and weakness leading to long-term disability. Lately, targeted gene therapy has emerged, so that genetic diagnosis might be the basis of treatment.

Objective. We analyze the case of a male child suspected of having Duchenne muscular dystrophy and his dystrophin gene variants.

Method. We present the case of a 6 year old boy who presented at two years of age increased values of hepatic transaminases of an unknown etiology. At three years of age he developed muscle weakness and cramping, mild calf hypertrophy and he was found with increased levels of serum alanine transaminase and aspartate transaminase, together with markedly elevated levels of serum creatine kinase (20 times the upper

limit of normal). Later he developed positive Gowers' sign. Multiplex ligation-dependent probe amplification-based method (MLPA) was used to analyze dystrophin gene variants.

Results. By using MLPA method in our patient dystrophin gene deletions were identified between exons 46 and 52. He did not presented dilated cardiomyopathy or arrhythmias. Deflazacort treatment was postponed.

Conclusions. The applicability of exon skipping drugs depends on the specific mutational frequencies within populations. Our patient data, similar to other cases, suggest that for numerous patients, multiple exon skipping between exons 46 and 52 could potentially be a target for exon skipping therapy.

Alpha 1-antitrypsin deficiency

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Alpha 1-antitrypsin deficiency (AATD) is one of the most prevalent autosomal recessive inherited disorders, which is associated with an increased risk of developing pulmonary emphysema and liver disease. Pulmonary emphysema is more likely to be presented in patients who have a history of smoking, however, non-smokers may develop progressive lung disease as well. More than 100 genetic variants have been described.

PiZZ homozygous genotype is by far the most well-known severe deficiency state that is strongly linked to serious extrapulmonary clinical findings such as liver cirrhosis, hepatocellular cancer, vasculitis and panniculitis.

If serum levels of α 1-antitrypsin are decreased, this will lead to low alveolar concentrations, where the α 1-antitrypsin molecule normally would serve as protection against proteases such as neutrophil elastase. The resulting protease excess in alveoli destroys alveolar walls and causes emphysema.

Lung disease in AATD has an earlier onset than "usual" COPD and may be misdiagnosed as asthma.

The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Moreover, quantitative deficiency must be supported by qualitative tests to identify the genetic mutations causing AATD.

FEV1 has been used as the major indicator for the presence, progression and severity of lung disease. However, FEV1 is a poor surrogate of emphysema, while gas transfer is more specific. Therefore, CT densitometry has been established as the most specific and sensitive surrogate end-point for the evaluation of therapeutic benefit of augmentation therapy.

Management of symptomatic lung disease is very identical to usual COPD, including inhalers, pulmonary rehabilitation, and avoidance of risk factors such as smoking. Infusion of plasma-derived AAT (augmentation therapy) is the only approved disease-specific treatment known to restore or persevere the physiological levels of the damaged lung.

Diagnosis and treatment of pulmonary alveolar proteinosis

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Pulmonary alveolar proteinosis (PAP) represents a rare pathology, affecting 3.7 up to 40 cases per million, depending on the geographic area. Also known as pulmonary alveolar phospholipoproteinosis, the disease is characterized by the progressive accumulation of surfactant, and the main symptoms are dyspnea and cough, in severe cases respiratory failure might be present, with/without cyanosis and/or digital clubbing. Classification of PAP includes 3 forms, based on pathogenetic mechanisms. Autoimmune PAP, also called primary PAP- represents about 90% of all cases, and is determined by the presence of anti-granulocyte macrophage-colony stimulating factor (GM-CSF) antibodies. Secondary PAP occurs post toxic-inhalation, in certain infections or is associated with hematologic, metabolic diseases or cancer. Congenital PAP is caused by genetic disorders of surfactant production or surfactant metabolism. Chest X-ray, Computed tomography serve as complementary examinations in a clinical context, but the final diagnosis can be made only after bronchioloalveolar lavage, followed by periodic acid Schiff (PAS) staining is performed. The detection of Anti GM-CSF antibodies is useful when investigating autoimmune PAP, ELISA being the gold-standard method. In terms of therapeutic options, whole lung lavage or local lobe lavage represents an accesible method that could improve survival and quality of life, supplemental GM-CSF therapy (inhaled or subcutaneous) is controversial, immunosuppressive therapy and plasmapheresis represent alternative therapeutic methods, but with modest results. We present a case report of a young immunocompetent patient, with persistent cough and progressive dyspnea, diagnosed with PAP and a favourable evolution in 2 years follow-up.

A rare case of cystic fibrosis in an adult patient

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Introduction. Cystic fibrosis (CF) is the most common autosomal recessive disorder in the Caucasian population. The c.2657+5G>A(c.2789+5G>A) mutation has a frequency of 0.38% and c.1624G>T(p.Gly542Ter) mutation has a frequency of 2.64% in a reference group of patients clinically diagnosed with cystic fibrosis.

Case report. A 28 year old female patient with the diagnosis of bilateral upper lobe bronchiectasis, partially controlled bronchial asthma (4th step of treatment), with multiple infectious and allergic exacerbations, chronic rhinitis and nasal polyposis. The patient presents with a pathological history of apical right pachypleuritis, post TBC sequelae in the upper right lobe and left parahilar area, and is suspected of sinus tachydia. The ample pulmonary pathology raised the suspicion of an atypical case of cystic fibrosis, which warranted the genetic analysis of the patient. This was carried out through a hybridization technique, using the CF StripAssays®-ViennaLab Diagnostics GmbH commercial kit. This method allows for the detection of the most common 34 CFTR mutations, as well as the polyT variant (5T/7T/9T) in intron 8.

Results. The result of the strip assay revealed a compound heterozygote G542X+2789+5G>A.IVS8 5T/7T/9T polymorphism-7T/9T heterozygote (benign polymorphism) genotype.

Conclusions. The CF StripAssay method analyses 34 of the 1900 mutations identified so far in CF patients, and is capable of diagnosing rare compound heterozygous cases-such as the one presented here. While the strips investigate an adequate array of mutations, the clinical aspects of the case dictate whether we should proceed with further investigations, such as sequencing.

Hypoglycemic coma and cardio-respiratory arrest - clinical presentation in 3-hydroxy-3-methylglutaric aciduria in infant

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Introduction. 3-Hydroxy-3-methylglutaric aciduria (3-HMG) is a rare autosomal recessive metabolic disorder caused by a deficiency of 3-hydroxy-3-methylglutaryl-CoA lyase. This enzyme is involved in leucine metabolism and ketone body synthesis. Its absence could be associated with severe episodes of vomiting, neurological symptoms, hypoglycemia and metabolic acidosis without ketonuria. The disease is usually present in newborns and infants, being triggered by infections or fasting.

Case report. We are presenting the case of a 9-month-old male, born from a consanguineous family, with two previous admissions in a local hospital for coma, seizures and cardio-respiratory arrest, with severe hypoketotic hypoglycemia (2 mg/dl, respectively 4 mg/dl), severe metabolic acidosis and abnormal liver function tests. During the first evaluation in our hospital, after treatment from local hospital, the specific investigations were not compatible with a metabolic disorder. Two months later, during an infectious episode, the child presents again hypotonia and coma. NMR spectroscopy detected high levels of 3-hydroxy-3-methylglutaric, 3 hydroxy isovaleric and 3 methyl glutaric acids and other metabolites specific for 3-HMG. Cerebral MRI showed diffuse changing of the signal at the level of the white matter, dentate nuclei and tegmental tracts. Prompt treatment with glucose infusion and rapid correction of acidosis were essential for the survival of this child and good evolution during follow-up.

Conclusions. 3-HMG has a poor prognostic in the absence of early measures. The metabolic lab tests performed in the crisis could lead to the correct diagnosis. Early treatment will prevent severe episodes of decompensation and neurological lesions possible on the long-term.

Nutritional support in mitochondrial diseases in children

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Mitochondrial diseases (MDs) are a large group of rare diseases caused by innate defects of genes that encode the synthesis of proteins involved in cellular energy metabolism. Although they have high genetic heterogeneity and a highly variable clinical expression, mitochondrial diseases have a common pathogenetic mechanism: insufficient energy production in the mitochondria.

For nutritionists, MDs are a challenge. The child with MD has an increased nutritional risk score for both malnutrition and obesity. Standard restrictive diets useful in the treatment of other inborn errors of metabolism are often ineffective, because mitochondrial diseases involve genetic defects common to the metabolism of sugars, fatty acids and amino acids.

The main dietary recommendations are: avoiding prolonged fasting which can have extremely serious consequences, small snacks between main meals, low fat content, special measures under stress conditions. In the nutritional support scheme, antioxidant agents and enzymatic cofactors are often associated.

Role of imaging in the diagnosis of disorders of sexual development

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Learning objectives. To demonstrate the role of imaging methods in the assessment of disorders of sexual development and their associated anomalies.

Background. Disorders of sexual development are rare conditions, associated with different genetic diseases which may show a similar phenotype. In such cases the role of the radiologist is to answer questions like: Are there male or female gonads present and what is their location and appearance? Are there associated malformations? The answer to these questions determines the need for further investigations and surgical planning if needed.

Imaging techniques and findings. Imaging in patients with DSD should be tailored according to each clinical situation, avoiding as much as possible invasive procedures.

The first line investigation is represented by ultrasonography as it is able to document the anatomy and location of the gonads, evaluate if their structure and location is normal and to assess associated anomalies. The evaluation of the adrenals is also mandatory when there is a suspicion of congenital adrenal hyperplasia.

If US cannot answer all these questions, additional imaging (genitography, MRI) is necessary.

Conclusion. Imaging of DSD is a challenge for the radiologist because of the large spectrum of anomalies of the genitalia and their associated malformations. Ultrasonography is the first line imaging technique and most often it provides all the necessary information, but sometimes additional investigations may be needed.

Genotype-phenotype relationship in Prader-Willi syndrome

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Prader Willi syndrome (PWS) is a rare and complex genetic disease, with numerous implications on metabolic, endocrine, neurologic systems, with behavior and intellectual difficulties. It is caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13: paternal deletion of the 15q11-q13 region; maternal uniparental disomy 15; or imprinting defects. Different genotypes in PWS

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leading to a quite similar phenotype with infantile hypotonia with failure to thrive, short stature, small hands/feet and hypogonadism/hypogenitalism due to growth and other hormone deficiencies, hyperphagia with obesity and cognitive and behavioral problems including obsessive compulsions, tantrums and self-injury.

We reviewed six cases confirmed PWS on phenotype, endocrine and metabolic changes. All of these patients are characterized by severe hypotonia with feeding difficulties in the first years of life. Global developmental delays, hyperphagia with a gradual development of morbid obesity at about three years of age. It is also recognizable by facial features, strabismus, and other musculoskeletal conditions. They also manifest short stature, hypothalamic dysfunction, hypogonadism, hypothyroidism. The recommended therapeutic interventions shown to be useful for improvement of length and physical ability.

Conclusion. The early diagnosis and management of individuals with Prader-Willi syndrome is important for anticipating and managing or modifying complications associated with this rare disorder.

Prenatal genetic diagnosis of ethylmalonic encephalopathy in a Romanian family

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Ethylmalonic encephalopathy (EE) is a very rare and severe autosomal recessive metabolic disorder of infancy affecting the brain, gastrointestinal tract, and peripheral vessels. The signs and symptoms of EE are apparent at birth or begin in the first few months of life, and become worse in time, so most affected individuals survive only into early childhood. EE is caused by homozygous or compound heterozygous mutation in the ETHE1 gene (located on chromosome 19q13) which encodes a mitochondrial matrix protein. This gene provides instructions for making an enzyme that is active in mitochondria, which breaks down sulfide, a molecule that is critical at very low levels for normal cell functioning but is toxic at high levels. Excess sulfide interferes with numerous cell activities, including mitochondrial energy production. We present a rare case of a couple diagnosed as heterozygote carriers of a pathogenic mutation in exon 5 of ETHE1 gene (c.554T>G; p.Leu185Arg) through WGS sequencing, after the death of their first born, presumably due to a mitochondrial disease. During the second pregnancy, the genetic testing on amniotic fluid revealed that the fetus is homozygote for the aforementioned pathogenic mutation. Genetic testing on family members identified the sister of the pregnant woman, as a heterozygote carrier for the same mutation. Since only 70 individuals with this condition have been identified worldwide, mostly in Mediterranean and Arab populations, we consider this case to be very interesting both from clinical and also genetic aspects.

The diagnostic contribution of high resolution manometry in rare digestive diseases

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Esophageal high resolution manometry (HRM) is performed to record the mechanically relevant aspects of the swallow in order to gain insight into esophageal (patho)physiology and to correlate patient symptoms with the observed manometric patterns, in order to improve the accuracy of diagnosis.

We present you several (rare) cases in which esophageal HRM was performed in order to establish the correct diagnosis. We usually perform esophageal HRM in all our patients with dysphagia, non-cardiac chest pain, heartburn, regurgitation, belching if the findings in other investigations are not compatible with the complaints of the patients (gastroscopy, abdominal ultrasound, abdominal CT). The protocol that we used was 10 wet swallows, 5 ml each, then 5 rapid swallows, then 200 ml free drinking test. The device that we used was produced by Diversatek Healthcare (Sandhill Scientific) and the software for data analysis was Zvu® Advanced Diagnostic GI Software. The probe was a 32 channel pressure, 16 impedance from UniSensor (regular value IRPm – 28 mmHg). Chicago Classification v3 was used to interpretate the findings.

We identified achalasia in 4 patients, 2 with type 1 achalasia and 2 with type 2 achalasia, Esophagogastric junction outflow obstruction in 4 patients and Jackhammer esophagus in 2 patients.

We also performed esophageal HRM to a series of patients with rare disease in order to exclude any motility disorder: eosinophilic esophagitis – 1 patient, celiac disease – 1 patient, gastric neuroendocrine tumor type 1 – 1 patient.

Esophageal HRM is a very useful test, mandatory in the algorithm of investigating rare diseases in gastroenterology.

Gaucher disease – a rare cause of hepato-splenomegaly

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Gaucher disease - short history. Gaucher disease is a genetic disorder with autosomal recessive transmission, due to the deficiency of the glucocerebrosidase enzyme by the defect of the GBA1 gene and resulted in the accumulation of glycolipids in different tissues. The disease belongs to a group of diseases called lysosomal treasures and is more common in Ashkenazi Jewish descendants, affecting 1: 855 persons; in the rest of the population the disease affects 1: 40,000 people. There are several different types of Gaucher disease, but the most common type is 1 (about 90% of cases). Patients with type 1 initially notice pain-free splenomegaly, anemia or ecchymosis and bleeding due to thrombocytopenia and skeletal impairment.

The diagnosis of certainty is based on the measurement of the activity of the glucocerebrosidase enzyme and a value <15% of the normal is diagnostic.

There is no cure for Gaucher disease, but currently there are enzyme replacement treatments administered i.v at 2-week intervals and the prognosis of patients with

type 1 Gaucher disease is very good, a study estimated a life expectancy of 68 years vs. 77 years in the general population.

Case presentation. The clinical case refers to the PV patient, 51 years old, male, urban environment, non-smoker, not consuming alcohol, but known since 1976, with RAA and with a hepato-splenomegalic syndrome whose etiology cannot be specified. Performs the first puncture liver biopsy with inconclusive result for a certain condition and remains in observation for hepato-splenomegaly.

In 1994 he repeated the puncture of liver biopsy → aspect of chronic active hepatitis.

In December 2004, he was admitted to the Gastroenterology and Hepatology Clinic SCJUT Timisoara for pain in the right hypochondrium, marked asthenia, fatigue, pyrosis, post-enlargement bloating and evaluation of hepato-splenomegaly. Liver biopsy puncture is performed with histopathological examination: hepatocytes with turbid intumescence and sometimes clear, liver sinusoids occupied by large cells with pale cytoplasm, fibrillar appearance, central nucleus or prominent eccentric = Gaucher cells and the diagnosis of Gaucher disease is confirmed.

In Feb. 2007, the patient is referred to the Cluj Genetic Diseases Center for completing investigations with specific enzymatic determinations, namely: β -glucocerebrozidase = 0.92 nmol / h / mg protein (VN = 6-25) and Chitotriosidase = 87,500 nmol / h / Plasma ml (VN = 170-5700), Genotype: N370S / N370 S. The low net value of β -glucocerebrozidase and increased Chitotriosidase confirms the diagnosis of Gaucher disease (type 1). Chronic enzyme replacement therapy with Imiglucerasum (Cerezyme) is recommended as the only effective therapy, at a minimum dose of 31 IU / kg, at a dose interval of 2 weeks (2800 U / infusion). Under substitution treatment, the initial clinical-biological evolution of the patient is favorable, with repeated hospitalizations in the Gastroenterology Clinic for evaluation and correction of anemic syndrome.

In 2017 - the evolution of the patient 10 years after the initiation of the enzymatic substitution treatment shows the achievement of the therapeutic objectives, with clinical, biological improvement, of the markers of the activity of the disease, respectively imaging.

The patient continues the treatment with Cerezyme and enzymatic and genetic tests are carried out within the family members: the mother and the sister are detected with mild forms of Gaucher disease.

Markers of disease activity - decreasing: Lyso GL1: 74.6 ng / dl (2017) → 51.1 ng / dl (2018) → 34.4 ng / dl (2019) and Cyp 2D6 = fast metabolizer (25.10. 2017).

In 2018 and 2019, the patient continues the chronic enzyme replacement therapy with Cerezyme, 3600 u / dose (30 u / kg), an i.v infusion every 2 weeks, the dose being adapted to the patient's weight. The semester control is also continued, alternatively at the Medical Clinic 2 Cluj, respectively the Timisoara Emergency Clinical Hospital, the Gastroenterology and Hepatology Clinic.

The genetic counseling of family members of patients with Gaucher disease and screening for the presence of genetic mutations will be considered.

Clinical and genetic considerations in two cases of Sotos syndrome

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Sotos syndrome is a rare hereditary disease with an estimated frequency of 1:15000 live births. It has autosomal dominant inheritance and more than 95% have a *de novo* pathogenic variant; it is characterized by a distinctive cranio-facial dysmorphism, intellectual disability and overgrowth.

We are describing two clinical cases of Sotos syndrome followed in our Medical Genetic Service, focusing on the clinical and genetic particularities.

Case #1: Female patient, first presentation at five months old. The clinical examination identified excessive statural growth and cranio-facial dysmorphism (macrocephaly, dolichocephaly; broad, prominent forehead; long, narrow face; long palpebral fissures with a mild antimongoloid orientation; prognatism). Currently, the patient is two years old and presents both intellectual and motor disability, as well as a congenital heart malformation and a persistent urinary infection. The genetic tests (SNP-Array and MLPA) reveal a deletion of 3.8 Mb on the fifth chromosome (5q35.2 – 5q35.3).

Case #2: Female patient, first presentation at the age of 12; she presented somatic gigantism, cranio-facial dysmorphism (macrocephaly, broad forehead; long face; hypertelorism; ogival palate, prognatism) and intellectual disability. The clinical examination, imaging and laboratory tests revealed hypothyroidism and a very large pelvic tumor. Following surgical intervention and histopathological testing, the tumor has been identified as a dermoid cyst.

Genetic testing is in progress.

Conclusions. Focusing on the anamnestic, somatic and functional particularities in the described cases, both patients have been diagnosed with Sotos syndrome. The discussion is about the importance of clinical examination and genetic testing in identifying the genotype - phenotype correlation.