18th Conference of the Polish Association for the Study of the Liver

11-13 June 2015
Mikołajki

Programme and abstracts

Programme

11 June, Thursday

15.00–15.05 **Opening ceremony**
Robert Flisiak

15.05–15.15 **Annual activity report of the Polish Association for the Study of the Liver**
Jerzy Jaroszewicz

15.15–15.20 **Awarding ceremony**
Robert Flisiak

15.20–16.10 **INAUGURAL SESSION**
Robert Flisiak

15.20–15.45 **Finding the right treatment for the right patient with HCC**
Markus Peck-Radosavljevic

15.45–16.10 **Gut–liver axis in health and disease**
Jacek Juszczyk

16.10–17.40 **PLENARY SESSION 1**
NON-ALCOHOLIC FATTY LIVER DISEASE
Dariusz Lebensztejn, Marek Hartleb

16.10–16.30 **Pathogenesis of nonalcoholic fatty liver disease**
Michał Kukla

16.30–16.50 **Liver biopsy and non-invasive diagnostic tools in non-alcoholic fatty liver disease**
Dariusz Lebensztejn

16.50–17.10 **Treatment of NAFLD**
Piotr Socha

17.10–17.30 **Non-alcoholic fatty liver disease – internist perspective**
Marek Hartleb

17.30–17.40 **Diagnosis of liver steatosis and fibrosis using transient elastography in children with non-alcoholic fatty liver disease**
Wojciech Jańczyk, Anna Świąder-Leśniak, Aldona Wierzbicka-Rucińska, Piotr Socha

17.40–18.00 Coffee break

18.00–18.30 **SPONSORED SESSION 1 – (BMS) Bristol-Myers Squibb**

20.00 Dinner

12 June, Friday

08.00–09.30 **PLENARY SESSION 2**
BARRIERS IN HEPATOLOGY CARE
Krzysztof Tomasiewicz, Tadeusz Łapiński

08.00–08.20 **Diagnosis of liver diseases in primary care and specialized health care**
Krzysztof Tomasiewicz

08.20–08.40 **Access to treatment of chronic hepatitis C in Poland and in other European Union countries**
Robert Flisiak

08.40–09.00 **Keeping the patient in the drug program – benefit or economic loss for the hospital?**
Michał Chrobot

09.00–09.20 **The role of nurses in the diagnosis and treatment of patients with chronic viral hepatitis**
Tadeusz Łapiński

09.20–09.30 **Financing of the treatment costs of HCC patients in Poland**
Olga Krupińska, Dariusz Wasiak, Andrzej Śliwczyński, Jarosław Czerwiński, Bożena Walewska-Zielecka, Marta Hreńczuk, Maurycy Jonas, Beata Łągiewska, Wojciech Lisik, Piotr Małkowski

09.30–09.45 Coffee break

09.45–10.45 **SPONSORED SESSION 2 – ABBVIE**

10.45–11.55 **PLENARY SESSION 3**
SURGICAL TREATMENT OF LIVER DISEASES
Piotr Małkowski, Krzysztof Zieniewicz

10.45–11.05 **Intrahepatic cholangiocarcinoma (iCC) – current standards in diagnosis and surgical treatment**
Krzysztof Zieniewicz

11.05–11.25 **Hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) – diagnosis and treatment**
Piotr Małkowski

11.25–11.45 **Rare liver diseases – indications for LTx**
Marek Pacholczyk

11.45–11.55 **Surgical treatment of HCC patients – one center experience**
Maurycy Jonas, Dariusz Wasiak, Michał Mańkowski, Olga Krupińska, Marek Pacholczyk, Beata Łągiewska, Piotr Małkowski, Andrzej Chmura

11.55–13.25 **PLENARY SESSION 4**
CASE STUDY SESSION
Andrzej Habior, Joanna Pawłowska

11.55–12.35 **Hepatosplenomegaly, hypersplenism, portal hypertension with esophageal varices – are they always a sign of liver cirrhosis?**
Joanna Pawłowska, Joanna Cielecka-Kuszyk

12.35–13.15 **Young overweight woman with metabolic disorders, PCOS and laboratory signs of liver damage**
Andrzej Habior, Andrzej Gabriel

13.15–13.25 **Discussion and conclusions**

13.25–14.25 **SPONSORED SESSION 3 – GILEAD**

14.25–15.30 Lunch

15.30–17.00 **PLENARY SESSION 5**
HCV INFECTION
Robert Flisiak, Waldemar Halota

15.30–15.50 **If not hepatitis A and not hepatitis B, then hepatitis C**
Waldemar Halota

15.50–16.10 **HCV and diseases of civilization**
Anna Piekarska

16.10–16.30 **Prospects for availability of innovative HCV therapies in Poland**
Andrzej Horban

16.30–16.50 **Alcoholic liver disease and HCV infection**
Anna Boroń-Kaczmarska

16.50–17.00 **Efficacy and safety of 12 weeks of simeprevir (SMV) plus peg-interferon and ribavirin (PR) in five clinical studies: a pooled subset analysis of Polish patients with genotype 1 (GT1) hepatitis C virus (HCV)**
Andrzej Horban, Ewa Janczewska, Dorota Zarębska-Michaluk, Waldemar Halota, Robert Flisiak, Karin Weber, Michael Schlag, Ceyhun Bicer, James Witek, Ralph DeMasi

17.00–17.15 Coffee break

17.15–17.45 **SPONSORED SESSION 4 – ROCHE**

17.45–19.15 **PLENARY SESSION 6**
HBV INFECTION
Małgorzata Pawłowska, Jerzy Jaroszewicz

17.45–18.05 **Novel trends in biology and immunology pertaining to HBV infections**
Iwona Mozer-Lisewska

18.05–18.25 **Prophylaxis of vertical HBV infections**
Małgorzata Pawłowska

18.25–18.45 **The road to HBV-elimination from the host, can cccDNA be eradicated?**
Jerzy Jaroszewicz

18.45–19.05 **Occult hepatitis B infections**
Piotr Grabarczyk

19.05–19.15 **Chronic HBV infection alters monocytes subpopulations and monocytic CD163 expression**
Anna Parfieniuk-Kowerda, Andrzej Eljaszewicz, Magdalena Świderska, Kamil Grubczak, Paula Mikłasz, Jerzy Jaroszewicz, Marcin Moniuszko, Robert Flisiak

20.00 Dinner

13 June, Saturday

08.30–09.00 **SPONSORED SESSION 5 – JANSSEN**

09.00–10.30 **PLENARY SESSION 7**
LIVER ENCEPHALOPATHY
Marek Woynarowski, Anatol Panasiuk

09.00–09.20 **Neuropsychiatric assessment in a person with liver encephalopathy**
Alina Borkowska

09.20–09.40 **Minimal hepatic encephalopathy: truly a minimal problem?**
Piotr Milkiewicz

09.40–10.00 **Treatment of hepatic encephalopathy**
Anatol Panasiuk

10.00–10.20 **The role of hepatic encephalopathy in children in qualification for liver transplantation**
Irena Jankowska

10.20–10.30 **Diagnosis of minimal hepatic encephalopathy (MHE) by Psychometric Hepatic Encephalopathy Score (PHES) or critical flicker frequency (CFF) is associated with liver cirrhosis progression in the follow-up**
Agnieszka Stawicka, Justyna Zbrzeźniak, Natalia Kilisińska, Aleksandra Świderska, Mateusz Panasiuk, Tadeusz W. Łapiński, Jerzy Jaroszewicz, Robert Flisiak

10.30–10.45 Coffee break

10.45–11.15 **SPONSORED SESSION 6 – MSD**

11.15–12.45 **PLENARY SESSION 8**
DRUG-INDUCED HEPATOTOXICITY
Krzysztof Simon, Włodzimierz Mazur

11.15–11.35 **Hepatotoxicity of drugs – etiopathogenesis, clinical and pathomorphological classification**
Krzysztof Simon

11.35–11.55 **Cholestatic drug-induced liver injury**
Włodzimierz Mazur

11.55–12.05 **Severe cholestatic liver injury in a fitness-obsessed white collar**
Monika Pazgan-Simon, Anna Machaj

12.05–12.20 **Statins and fibrates and hepatotoxicity**
Maciej Jabłkowski

12.20–12.35 **Acetaminophen-induced hepatotoxicity**
Sylwia Serafińska

12.35–12.45 **Renal impairment in patients with chronic hepatitis C treated with first generation protease inhibitors**
Dorota Kozielewicz, Dorota Dybowska, Kornelia Karwowska, Magdalena Wietlicka-Piszcz

12.45–13.00 **Closing remarks**
Robert Flisiak

13.30–15.30 Lunch

ORAL PRESENTATIONS

The abstracts are printed in the form sent by authors, accepted by the Scientific Programme Committee.

INAUGURAL SESSION

Gut–liver axis in health and disease

Jacek Juszczyk

Prof. emer. (Poznan University of Medical Sciences)

There is an emerging evidence that gut microbiota plays an important role in pathogenesis of the liver diseases with clinical implications. Qualitative as well as quantitative changes have been described in a number of liver diseases, like nonalcoholic fatty liver disease (NAFLD), non-alcoholic steato-hepatitis (NASH), alcoholic fatty liver disease (AFDL), alcoholic liver disease (ALD), cirrhosis of the liver and intestinal failure – associated liver disease (IFALD). Small intestinal bacterial overgrowth (SIBO) has been described to be very common in liver disease. In normal conditions bacteria or bacterial metabolites are eliminated from the portal vein by Browicz-Kupffer cell. In liver failure gut-mucosal barrier is damaged. Large amounts of bacteria enter the liver with direct effects of products of gut bacterial metabolism. Immune response to a normal or abnormal microbiota is induced with synthesis of proinflammatory cytokines such as IL-1β, TNF and IL-6. Hepatic encephalopathy (HE) as a result of liver failure has been related to gut bacteria and inflammation in the setting of intestinal dysfunction. Systemic inflammation results in exacerbation of symptoms of HE, because proinflammatory reaction may act synergistically with ammonia in producing cognitive impairment of varying degree. The most common infection in cirrhosis is spontaneous bacterial peritonitis, and bacteria of gut origin are the most commonly isolated causative organisms. Antibiotics are commonly used in the management of the infectious complications of liver disease. The potential of microbiome-based therapeutics including second personalized probiotics and prebiotics have been reported for gut microbiota pharmacological modulation.

PLENARY SESSION 1
NON-ALCOHOLIC FATTY LIVER DISEASE

Pathogenesis of nonalcoholic fatty liver disease

Michał Kukla

Department of Gastroenterology and Hepatology, School of Medicine in Katowice, Medical University of Silesia in Katowice, Poland

Nonalcoholic fatty liver disease (NAFLD) is the most common hepatic disease in developed countries, due to its incontestable relationship with the metabolic syndrome, the prevalence of which is still increasing. The more advanced form of NAFLD, nonalcoholic steatohepatitis (NASH), is characterized by inflammatory infiltration and hepatocellular damage, with or without fibrosis. Hepatic fat accumulation generates inflammatory signals, oxidative stress and reactive oxygen species that can enhance liver injury and stimulate fibrosis. The development of NASH result from a complex interaction between the environment, represented by a sedentary lifestyle and excessive calories intake, and genetic factors, that are responsible for both the development of excess adiposity and its consequences. In 2010, a complex model, the "multiparallel hits" hypothesis, was introduced to explain NAFLD pathogenesis. According to this theory, the adipose tissue and gut-related factors play a pivotal role in the initiation of hepatic inflammation, suggesting that simple steatosis and NASH might be two different disturbances. This theory also incorporates new, non-hepatic players into the mechanisms of NAFLD and its progression. More advanced fibrosis parallels the number of components of the metabolic syndrome, which are strictly associated with disease progression. The majority of patients presenting with NASH have metabolic abnormalities, including insulin resistance/type 2 diabetes, obesity, dyslipidemia, and hypertension. Moreover, there are growing body of evidence suggesting an emerging role of bacterial overgrowth and gut flora alteration in NASH pathogenesis.

Explanation of the molecular and genetic basis of NAFLD will allow us appropriate management and treatment, which may prevent potential complication.

Liver biopsy and non-invasive diagnostic tools in non-alcoholic fatty liver disease

Dariusz M. Lebensztejn

Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok

Nowadays non-alcoholic fatty liver disease (NAFLD) is becoming the most common chronic liver pathology both in adults and children. Due to the coexistence of visceral obesity, insulin resistance and dyslipidemia, NAFLD is considered to be the hepatic manifestation of metabolic syndrome. NAFLD manifestation ranges from a simple liver steatosis to steatohepatitis (NASH), which may progress to advanced fibrosis, cirrhosis and end-stage liver disease. In clinical practice, the diagnosis of NAFLD is based on simultaneous confirmation of elevated alanine aminotransferase levels and demonstration of hepatic steatosis by imaging methods (ultrasound, magnetic resonance imaging) as well as the exclusion of other causes of liver steatosis such as chronic viral infections (HCV, HBV), toxic effects of alcohol or drugs, autoimmune liver diseases (AIH) and choosen metabolic disorders. Liver biopsy is required for definitive diagnosis of NAFLD (especially NASH) but it is not recommended as a screening test. Although there are defined indications for liver biopsy (exclusion of other liver diseases, suspicion of the advanced liver disease, before pharmacological or surgical treatment and in clinical trials), there is an urgent need to replace this method with non-invasive procedures which can be more useful to predict the degree of liver steatosis and fibrosis in fatty liver disease related to obesity. Transient elastography appears to be a promising tool for non-invasive assessment of liver fibrosis. Moreover, new serum biomarkers (or non-invasive panels) have been developed to assess the degree of steatosis, inflammation, fibrosis, and the risk of progression of NAFLD to the end-stage liver disease.

Treatment of NAFLD

Piotr Socha, Wojciech Janczyk

The practical question concerning NAFLD relates to treatment vs. no-treatment natural course of the disease. There are only few studies presenting longitudinal observations of adult patients with NAFLD and one pediatric cohort study which clearly show progression of the disease to cirrhosis in selected patients. In general we are not able to identify risk factors of disease progression (having NASH is a risk factor) and that is why therapy should be proposed to all patients. Weight loss is considered to be the most important treatment of this condition as it affects the entire cluster of the NAFLD-associated risk factors simultaneously. Physical activity also seems to play a major role in the treatment of NAFLD as it may ameliorate insulin resistance, maintain weight loss, improve liver histology and normalize ALT. Cochrane Collaboration has recently issued a systematic review on weight reduction in NAFLD and showed that restricted diet and physical exercise may be beneficial for NAFLD patients. On the other hand it has been shown that weight loss therapy is associated with a low rate of compliance (not exceeding 40%). Pharmacological treatment and dietary supplements are alternatives for patients with NAFLD in whom lifestyle change and/or weight loss was unsuccessful.

The authors of a few systematic reviews (Socha P., 2009; Musso G., 2010) were not able to identify effective and safe treatment for NAFLD. Some recent RCT studies further investigated pioglitazones, metformin and vitamin E. Sanyal *et al*. showed that vitamin E therapy resulted with higher rate of improvement in steatohepatitis than pioglitazone (43% vs. 19%, p = 0.001). Both drugs caused a small decrease in ALT and AST activity. In the TONIC trial which was conducted in children neither vitamin E nor metformin was superior to placebo in any of the major NAFLD outcomes.

In a recently published systematic review and meta-analysis of omega-3 LC-PUFA supplementation in adults with NAFLD Parker *et al*. (2012) claimed omega-3 LC-PUFA to be beneficial over placebo in reduction of liver fat (using liver biopsy, ultrasound or ^{1}H-MRS) and decrease of AST but the effect in ALT activity was not significant. Nobili *et al*. (2011) investigated the effect of supplementation of docosahexanoic acid (DHA) in children with NAFLD and showed a significant effect to reduce liver fat (assessed by abdominal ultrasound) and insulin resistance. However no effect was seen on ALT or body weight. We have just published another RCT study in children (Janczyk W., 2015) in which omega-3 fatty acids supplementation does not have a significant clinical effect in regard of the number of patients decreasing ALT activity, liver steatosis measured by ultrasound, but it improves AST and GGTP in children with NAFLD when compared to placebo and increase adiponectin level.

Probiotics and modifications of gut microflora could be another option of NAFLD therapy, still there are major concerns in respect of the methodology of the trials which raised this question. Interesting results came from the recent RCT trial by Alisi *et al*. (2014) in which he was able to prove a significant positive effect of probiotic mixture VSL#3 on body mass, liver steatosis and the effect was mediated by stimulation of GLP-1.

GLP-1 agonists, GFT505 (a combined PPAR-α/δ agonist), molecules activating simultaneously FXR and TGR5, obeticholic acid (OCA) and some other experimental therapies are under investigation and the first results are promising.

Non-alcoholic fatty liver disease – internist perspective

Marek Hartleb

Klinika Gastroenterologii i Hepatologii, Śląski Uniwersytet Medyczny w Katowicach

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of symptom-free increase of transaminasemia. In European populations NAFLD occurs in about 30% of persons. Diagnosis of NAFLD is based on liver ultrasound, features of metabolic syndrome, exclusion of alcohol overuse and liver disease of other etiology. In case of insulin sensitivity (normal result of HOMA test) the possible cause of liver steatosis are drugs, environmental toxins, familial hypobetalipoproteinemia, obstructive sleep apnea, inflammatory bowel diseases or endocrine diseases.

NAFLD is not uniquely a symptom of metabolic syndrome but also has unfavorable effect on the course of arterial hypertension, diabetes, atherosclerosis and heart function. Among patients with NAFLD histopathological features of steatohepatitis (NASH) occur with the frequency of 30-55%. Risk factors of NASH are age over 45 years, diabetes, obesity and AST/ALT ratio over unity. Mean survival in NASH is lower than in general population being associated with increased mortality from cardiovascular events, cancer or complications of portal hypertension. Advanced fibrosis (stage 3 and cirrhosis) is found in 8-23% of patients with NAFLD (about 3% of general population). *NAFLD fibrosis score* incorporating age, BMI, transaminases activity, diabetes or carbohydrate intolerance, thrombocyte count and albumin level (*online calculator*) is a valuable tool in detection of advanced fibrosis. Patients with NAFLD require multidirectional clinical assessment, including liver function and extrahepatic consequences of metabolic derangements. A NAFLD patient should be at least once consulted by specialist for exclusion of coexisting etiology of liver damage, detection of progressive potential of the disease, and establishing indications for monitoring or pharmacological therapy.

Diagnosis of liver steatosis and fibrosis using transient elastography in children with non-alcoholic fatty liver disease

Wojciech Jańczyk[1], Anna Świąder-Leśniak[2], Aldona Wierzbicka-Rucińska[3], Piotr Socha[1]

[1]Klinika Gastroenterologii, Hepatologii i Zaburzeń Odżywiania, Instytut „Pomnik – Centrum Zdrowia Dziecka" w Warszawie
[2]Zakład Antropometrii, Oddział Pediatrii, Instytut „Pomnik – Centrum Zdrowia Dziecka" w Warszawie
[3]Zakład Biochemii i Medycyny Eksperymentalnej, Instytut „Pomnik – Centrum Zdrowia Dziecka" w Warszawie

Aim of the study was to evaluate the relationship of liver tests, lipid metabolism markers and anthropometric mesurements with the liver stiffness (LSM) and Controlled Attenuation Parameter (CAP) using transient elastography Fibroscan®.

Material and methods: 125 overweight/obese children aged 14 ± 2.8 yrs with NAFLD, who presented with mildly increased transaminases, underwent liver stiffness (LSM) and steatosis (CAP) measurements using Fibroscan® as well as liver tests and lipid profile markers. In addition detailed anthropometric measurements were performed and their respective *z*-scores were calculated.

Results: Liver stiffness [kPA] was strictly related to ALT ($r = 0.46$), AST ($r = 0.43$), GGTP ($r = 0.22$), TG ($r = 0.31$), *z*-score BMI ($r = 0.39$), *z*-score waist ($r = 0.3$) and *z*-score for skinfolds. CAP [dB/m] correlated significantly with ALT ($r = 0.58$), AST ($r = 0.49$), GGTP ($r = 0.32$), TG ($r = 0.24$), *z*-score BMI ($r = 0.38$) and *z*-score for skinfolds. Multiple regression analysis showed that, among anthropometric parameters, best predictors for both liver stiffness (LSM) and steatosis (CAP) were *z*-score BMI and *z*-score triceps skinfolds. Laboratory tests that best predicted liver stiffness were total cholesterol, triglycerides and ALT while for liver steatosis they were triglycerides, LDL-cholesterol and ALT.

Conclusions: 1. Liver fat content measured by CAP and liver stiffness correlate strongly with liver tests, triglycerides and age- and gender-related anthropometric parameters. 2. BMI and triceps skinfolds best predicted fibrosis and steatosis when measured by Fibroscan. 3. Total cholesterol, triglycerides and ALT are the best predictors of fibrosis whereas triglycerides, LDL cholesterol and ALT are the best predictors for liver steatosis.

PLENARY SESSION 2
BARRIERS IN HEPATOLOGY CARE

Diagnosis of liver diseases in primary care and specialized health care

Krzysztof Tomasiewicz

Department of Infectious Diseases, Medical University of Lublin

Diagnosis of liver diseases may be difficult due to common lack of specific signs and symptoms. In other cases symptoms may be easily confused with different health problems. One must consider significant liver pathology even with lack of symptoms and in patients with normal "liver" tests. Especially primary care physicians may cause delay in appropriate diagnosis because of wrong interpretation of "correct" biochemical test results. The author's own experience and results of questionnaire study assessing GPs and specialists have shown poor knowledge of liver diseases. Improvement of physician postgraduate education is required. Self-reported lack of knowledge about different liver diseases, including viral hepatitis, congenital liver pathology, as well as very common in GPs practice NAFLD is confirmed by a number of studies and is consider a major barrier to managing these patients. Appropriate interpretation of some sensitive information from patient's medical records and history, risk factors as well as prompt referral to a liver specialist are essential. Development of guidelines should emphasize strategies for screening vulnerable populations, evidence based management and barriers to providing care.

Family doctors and specialists may be also confused about who is providing specialized care to liver disease patients. In Poland, hepatologists are mostly infectious disease doctors or gastroenterologists. In practice, many of both specialists avoid liver patients. Clarifying a structure of hepatologic care system would be helpful for all.

Access to treatment of chronic hepatitis C in Poland and in other European Union countries

Robert Flisiak

Klinika Chorób Zakaźnych i Hepatologii, Uniwersytet Medyczny w Białymstoku

In 2011 two initial direct acting antivirals (DAA) for treatment of chronic hepatitis C in combination with pegylated interferon alfa (PegIFN) and ribavirin (RBV) became available in some EU countries. Since availability of expensive drugs is driven usually by reimbursement policy, boceprevir (BOC) and telaprevir (TVR) become accessible for majority of european patients with some delay. This problem was a case not only for central and eastern Europe, but also for Italy, Spain, Greece and Portugal. Today, there are still several European, including UE countries (Bulgaria, Latvia, Romania, Russia, Slovenia, Ukraine) which reimburse PegIFN+RBV regimen only. Patients in other EU countries have access to BOC, TVR or SMV (simeprevir) based triple regimen, which is usually limited by hepatic fibrosis, history of previous treatment or IL28B genotyping applied as a criteria for triple therapy in Poland only. However in France, Germany, Austria and Scandinavia triple therapy was almost replaced in 2015 with IFN-free combination of sofosbuvir/ledipasvir or ombitasvir/parytaprevir/rytonavir/dazabuvir, which provide almost 100% efficacy and excellent safety profile. The crucial barrier for access to IFN-free regimen in other countries is price exceeding 40k EUR, but this will probably be removed in coming few years because of expected competition. The first signal just came from the Spanish Health Ministry, which despite of financial crisis decided to sign contracts with pharmaceutical companies for IFN-free regimen delivery. Therefore it looks like even Poland known of the lowest financing of HCV treatment in EU should reimburse this therapy by the end of this decade.

Keeping the patient in the drug program – benefit or economic loss for the hospital?

Michał Chrobot

Following the entry into force of the Act of 12 May 2011. On reimbursement of medicines, foodstuffs intended for particular nutritional and medical devices have significantly changed the rules of the contracts for drug programs. These changes have introduced a number of modifications in the area of clearing, while reducing the „profitability" of drug programs for hospitals. In his lecture, the author attempts to show that the correct implementation of drug programs, apart from the obvious benefit of the merits of patients, no negative financial consequences for the institution, and proper settlement services allows even to improve the financial condition of the departments implementing them.

The role of nurses in the diagnosis and treatment of patients with chronic viral hepatitis

Tadeusz Wojciech Łapiński

In 1955 Wirginia Henderson (American) defined the concept of nursing, which of late has been adopted by the International Council of Nurses as applicable throughout the world. This process has been defined as „Orderly and systematic way of determining the problems of human welfare, establishing plans to resolve them, implementation of these plans and assessing their effectiveness achieved in addressing the identified problems."

Currently, in most European countries and North America, there are numerous hepatology nurses associations that have developed a system of care for patients with chronic liver damage.

The activity of nurses in the diagnosis, treatment and care of the patient after treatment is on the same level parallel with the operation of doctors. The role of these two professional groups is different, however, in modern medicine determined not overlapping responsibilities.

The role of nurses in the diagnostic process is based on the daily assessment of the general condition of the patient, measuring vital signs, nutrition analysis, evaluating color and lesions of skin. The nurse is a person with often the first contact, allowing you to determine the mental state of the patient, as well as an assessment of the patient's knowledge about risk factors of the disease. Established procedures performed by nurses in the diagnostic and therapeutic procedures allow doctors to focus on their business, saving time and reducing the likelihood of errors.

The activity of nurses in therapeutic processes in the broad sense supervision and striving for adherence therapy, monitoring possible adverse effects, the initial reaction to these symptoms, inform doctor about situations which may affect the course of treatment.

Permanent broadening nurses' knowledge about new methods of diagnosis and treatment of patients with HBV or HCV infection, patient education should result in relation to the enhancement of health, the formation of a sense of responsibility for their own health and to raise awareness about the need for systematic monitoring of expertise.

Financing of the treatment costs of HCC patients in Poland

Olga Krupińska[1], Dariusz Wasiak[2], Andrzej Śliwczyński[3], Jarosław Czerwiński[2], Bożena Walewska-Zielecka[1], Marta Hreńczuk[2], Maurycy Jonas[4], Beata Łągiewska[4], Wojciech Lisik[4], Piotr Małkowski[2]

[1]Department of Public Health
[2]Department of Surgical and Transplant Nursing
[3]National Health Fund (NFZ)
[4]Department of General and Transplant Surgery, Medical University of Warsaw

Introduction: Along with the global increase in the number of new cases of HCC are growing expenditure on its treatment.

Aim of the study: Comparison of expenditures for the treatment of patients with HCC in the period: since 2008 through 2013.

Material and methods: Analysis of the data obtained from the National Health Fund (NFZ) and Poltransplant Liver Transplant Registry for the expenses associated with treatment of HCC patients with: liver resection – LR, radiofrequency ablation – RFA, chemoembolization – TACE, liver transplantation – LTx, chemotherapy/sorafenib therapy and palliative care (hospice).

Results:

2008 year:

Total no of pts: 1138.

Total costs – PLN; costs/pt: 7 593853.

LTx; No of pts/costs; 225000/pt: 13/2 936908.
LR, RFA, TACE; No of pts/costs; Costs/pt: 254/1 231336; 4847/pt.
Chemother/Sorafenib; No of pts/costs: 109/1 087537.
Hospice; No of pts/costs: 43/86900.
Other costs: 2 251172.
2013 year:
Total no of pts: 1745.
Total costs – PLN; costs/pt: 28 204681.
LTx; No of pts/costs; 225000/pt: 59/13 275000.
LR, RFA, TACE; No of pts/costs; Costs/pt: 575/6 138899; 10676/pt.
Chemother/Sorafenib; No of pts/costs: 183/5 509082.
Hospice; No of pts/costs: 110/297009.
Other costs: 2 984691.

Conclusions: Expenditures for treatment of patients with HCC have increased fourfold over 5 years. During the same period, the number of patients increased of 50%. Expenditures for surgical treatment have significantly increased, including LTX.

PLENARY SESSION 3
SURGICAL TREATMENT OF LIVER DISEASES

Intrahepatic cholangiocarcinoma (iCC) – current standards in diagnosis and surgical treatment

Krzysztof Zieniewicz

Department of General, Transplant & Liver Surgery, Medical University of Warsaw

Intrahepatic cholangiocarcinoma (iCC) is a subtype of heterogenous group of aggressive cancers arising from cholangiocytes or – as recently published – may also arise directly from transdifferentiation of hepatocytes. iCC are relatively rare, accounting for 20-25% of all biliary cancers, but with increasing incidence up to 8.5 per 1 000 000 population in last decades od 20th century in USA. Mortality from iCC also has risen, paralleling the rising incidence. Overall 3-year survival is 30% and 5-year survival – 18%. iCC may occur in patients with healthy liver or with underlying liver disease (HCV, steatosis), more likely in men, average age of diagnosis is 50 years old. Established risk factors for iCC are PSC, cholangitis, choledochal cysts, parasitic infection, infammatory bowel disease, drug and toxin exposure, cholelithiasis, bile duct adenoma or papillomatosis, alcoholic liver disease. ICC is aggressive, locally invasive tumor, often multifocal, with vascular invasion, lymphatic spread. The clinical presentation is usually nonspecific and symptoms can include abdominal pain or weight loss, sometimes jaundice. More than 50% of these tumors are unresectable at presentation. Incidental diagnoses of iCC in asymptomatic patients account for 12-30%.

Surgical resection is the only viable treatment option for patients with iCC. 5-year overall survival after surgery range from 17% to 44%, with medial survival 12-43 months. Nonsurgical therapies for iCC have not been demonstrated to improve survival or decrease the recurrence, however chemotherapy (cisplatin and gemcitabine) or radiation are sometimes offered as adjuvant therapy. Prospective data are needed to assess the efficacy the adjuvant therapies in this group of patients.

Hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) – diagnosis and treatment

Piotr Małkowski

Department of Surgical and Transplant Nursing, Medical University of Warsaw

Focal nodular hyperplasia (FNH) and hepatocellular adenomas (HCAs) constitute benign hepatic neoplasms in adults.

HCAs are monoclonal neoplasms characterized by an increased predilection to haemorrhage and also malignant transformation.

On the other hand, FNH is a polyclonal tumour-like lesion that occurs in response to increased perfusion. FNHs have no risk of haemorrhage or malignancy. Recent advances in molecular genetics and genotype-phenotype correlation in these hepatocellular neoplasms have enabled a new classification system. FNHs are classified into the typical and atypical types based on histomorphological and imaging features. HCAs have been categorised into four subtypes: (1) HCAs with HNF-1α mutations are diffusely steatotic, do not undergo malignant transformation, and are associated with familial diabetes or adenomatosis. (2) Inflammatory HCAs are hypervascular with marked peliosis and a tendency to bleed. They are associated with obesity, alcohol and hepatic steatosis. (3) HCAs with β-catenin mutations are associated with male hormone administration and glycogen storage disease, frequently undergo malignant transformation and may simulate hepatocellular carcinoma on imaging. (4) The final type is unclassified HCAs. Each of these except the unclassified subtype has a few distinct imaging features, often enabling reasonably accurate diagnosis. Biopsy with immunohistochemical analysis is helpful in difficult cases and has strong implications for patient management.

If diagnosis on FNH is confirmed no treatment is needed. In case of HCA usually liver recection is recommendet.

Rare liver diseases – indications for LTx

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Orthotopic liver transplantation is a life-saving procedure for patients with acute and chronic liver diseases. The major disorders, that are considered for liver transplantation include chronic liver disease with advanced cirrhosis, hepatocellular carcinoma and less common acute liver failure and liver-based metabolic defects. Chronic liver diseases that cause cirrhosis are by far the most common indication for liver transplantation (e.g. hepatitis C and hepatitis B, autoimmune hepatitis, alcoholic liver disease, cholestatic liver diseases: primary biliary cirrhosis, primary sclerosing cholangitis). In recent years primary liver tumor (HCC) joined the group most frequent indication for liver transplantation. Relatively common causes of acute liver failure include acute viral hepatitis, acetaminophen overdose (some countries e.g. United Kingdom), autoimmune hepatitis, drug induced liver injury, and sudden deterioration of Wilson disease. Rare indications for liver transplantation include Budd-Chiari syndrome, sarcoidosis, nonhepatocellular malignancies (e.g. epithelioid hemangioendothelioma, hepatoblastoma and metastases from endocrine tumors), parasitic diseases, metabolic disorders (e.g. non-alcoholic steatohepatitis, hereditary hemochromatosis), and congenital hepatobiliary disorders. Patients with familial amyloid polyneuropathy and primary hyperoxaluria are also rare potential candidates, as liver transplantation resolves the metabolic defect resulting in progressive extrahepatic disease. It is important to notice that conventional organ prioritization algorithms such as the Model for End-stage Liver Disease (MELD) score or Child-Pugh score may not adequately evaluate mortality risk in this group of potential organ recipients with rare liver diseases.

Surgical treatment of HCC patients – one center experience

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Introduction: Hepatic cell carcinoma (HCC) diagnosis and treatment increases in recent years. Most common etiology is hepatitis C. Therapy needs multidisciplinary team and treatment in specialized centers.

Material and methods: Our Department runs a program of diagnostics and surgical treatment of HCC and other liver tumors, since 2006. 310 patients were treated. HCC was identified in 159 cases. Diagnosis was based on USG, multiphase CT or NMR, according to BCLC. Radio frequency ablation (RFA) transcutaneus or through laparotomy was used in 53 cases, and tumor resection was used in 91 cases. Postoperative follow was based on radiological control in 3-6 months period as well as AFP level.

Results: In 93 cases recurrence was found after the operation. In 45 cases secondary surgery was conducted. 10 patients underwent LTx after tumor operation. The rest of patients were disqualified from surgical treatment, and were send to TACE or Nexavar treatment. The percentage of HCC recurrence is high. It needs systematic postoperative monitoring, with USG, CT or NMR scan. AFP may be used, but not as a single indicator. Qualification to RFA or resection as a bridge therapy for LTx or, as a final treatment needs to be defined.

PLENARY SESSION 5
HCV INFECTION

HCV and diseases of civilization

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The question of the association between HCV infection and diseases of civilization, most importantly atherosclerosis, has recently been increasingly raised by both epidemiologists and infectious diseases specialists. If we realize that chronic HCV infection exerts multidirectional proinflammatory effects, its association with diseases of civilization appears to be justified. Long-standing HCV replication in human body, including blood vessels, and virus-induced insulin resistance elicit oxidative stress in mesothelial cells. Moreover, proinflammatory cytokines production, cryoglobulinemia as well as increase in lipid peroxidation associated with liver steatosis may all contribute to systemic or regional inflammation of vascular cells. This kind of chronic blood vessels pathology can lead to atherosclerosis and subsequent increased prevalence of myocardial infarcts and strokes.

This hypothesis is being supported by the results of cross-sectional epidemiologic studies showing that chronic HCV infection is an independent risk factor of atherosclerosis, including carotid artery disease, in patients with and without coexisting liver steatosis. Moreover it has been proven that HCV infection is also an independent risk factor for cardiovascular events, e.g. stroke, and that there is a correlation between mortality and serum HCV viral load. The risk of developing carotid artery disease and myocardial infarct is higher in patients HCV-infected regardless their younger age and favorable cardio-metabolic profile. Compared to control group, patients with chronic hepatitis C are also at higher risk of death due to extrahepatic causes.

Above-mentioned evidence sheds new light on the pathogenesis of hepatitis C which seems to be not only a cause for liver impairment, but also a systemic infection. It is also an additional argument for increasing the efforts towards better detection of chronic HCV infection.

Alcoholic liver disease and HCV infection

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Alcoholic liver disease (ALD) and hepatitis C virus (HCV) infection represent, either alone or in combination, more than two thirds of all patients with liver disease in the Europe. The presentation summarized the basic informations concerning epidemiology, pathomechanisms and therapy of alcoholic liver disease in HCV infected persons.

ALD and HCV affect the progression of liver disease to liver cirrhosis and hepatocellular carcinoma (HCC) in a synergistic manner. The prevalence of anti-HCV is higher in alcoholics (10%) versus non-alcoholic patients; among cirrhotics with alcohol problem – about 10-14% are infected with HCV.

Mechanism of interaction between alcohol and HCV remain incompletely understood. Both factors can cause of full spectrum of ALD like steatosis, steatohepatitis, cirrhosis and, in some cases – hepatocellular carcinoma. Alcohol leads to steatosis by inducing lipogenesis while HCV caused steatosis by interruption of beta oxidation of fatty.

Several molecular mechanisms are also discussed that could explain the synergistic interaction of alcohol and HCV on disease progression. They include modulation of the immune response and apoptosis, increased oxidative stress via induction of CYP2E1 and the hepatic accumulation of iron.

From clinical point of view, factors that contribute to progression of ALD in HCV infected persons include the amount of alcohol consumed over a life time, drinking patterns, and nutritional status. Clinical picture of liver disease in patients with alcoholic problem and concomitant HCV infection is different, and in most cases the dominated symptoms are connected to alcohol. Unfortunately HCV infection is a contraindication for use of steroid treatment in alcoholic hepatitis patients albeit in other papers no significant difference was observed among HCV infected with alcoholic hepatitis treated with steroids. Alcoholics also have a decreased response rate to antiviral therapy which is most probably due to poor compliance.

Undoubtedly treatment of HCV positive alcoholic patients remains a clinical challenge a need further research.

Efficacy and safety of 12 weeks of simeprevir (SMV) plus peg-interferon and ribavirin (PR) in five clinical studies: a pooled subset analysis of Polish patients with genotype 1 (GT1) hepatitis C virus (HCV)

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Introduction: Pooled data from HCV GT1 treatment-naïve and -experienced patients enrolled in Poland (Polish subset) were analysed from five randomised, double-blind studies of SMV+PR (PILLAR, ASPIRE, QUEST-2, ATTAIN, and PROMISE).

Material and methods: Efficacy and safety data from the Polish subset of patients receiving SMV (150 mg once-daily) for 12 weeks plus 24-48 weeks of PR were analysed.

Results: 147 patients with HCV GT1 (GT1b: 95%) were included (median [range] age 37 [18-65] years; 59% male). Most patients were F0-F2 (86%) with baseline HCV RNA > 800 000 IU/mL (85%). Overall, 118 (80%) patients achieved sustained virologic response, 24 weeks after end of treatment (SVR24). Within this Polish subset, 47/53 (89%) treatment-naïve patients, 36/43 (84%) relapsers, 18/26 (69%) partial responders and 17/25 (68%) null responders achieved SVR24; SVR24 rates also varied according to IL28B genotype (p = 0.0494); CC: 96% [21/22]; CT: 80% [69/86]; TT: 67% [16/24]). During the first 12 weeks of treatment, 138/147 (94%) patients experienced AEs (59% worst Grade 1 or 2; 2% SAEs); most frequent AEs: pyrexia (53%), asthenia (25%) and neutropenia (23%). Three (2%) patients discontinued at least one study drug (1 [1%] SMV) due to an AE during the first 12 weeks.

Conclusions: SVR24 rates > 80% in treatment-naïve and relapser patients, and approaching 70% in non-responders were observed with SMV+PR in the Polish subset. Higher SVR24 rates were seen in patients with IL28B CC versus CT/TT genotype. SMV+PR was well tolerated and the AE profile in this Polish subset was consistent with overall Phase III findings.

PLENARY SESSION 6
HBV INFECTION

Novel trends in biology and immunology pertaining to HBV infections

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Hepatitis B remains a challenge, despite the decrease of new cases due to implementation of the effective vaccine. There are numerous studies devoted to the better understanding of the pathogenesis of the disease, in order to develop more specific and efficient therapies. Recent studies have shown, that Na^+-bile acid cotransporter (NTCP) is apparently a receptor mediating entry of HBV into the hepatocyte. As an confirmation, many interesting researches have been made.

HBV is a non-cytopathic virus. Liver damage is caused by the host immune response. It has been shown recently that there is a correlation between distinct HBV transcriptomes, being changed in the blood during the course of disease, and the innate immune response. This may require the need of reevaluation of clinical phases of the disease.

There are some novel research on factors influencing interferon production during HBV infection. Inter alia, it was discovered that both HBsAg and HBeAg, suppress MVP/MyD88 interaction and decrease type-I IFN production. Therefore, HBV may evade an immune response by limiting antiviral activity. Recent contributions also involve HCC pathogenesis in the course of chronic HBV infection. FOXP3 protein, the well-known inductor of regulatory T-lymphocytes, has been found in malignant hepatocytes. Viral preS2 region plays a role in transactivation of FOXP3.

According to the vast number of recently published studies in the field of biology and immunology of HBV, in spite of our increasing knowledge about the virus, there is still wide area for further research that may contribute to better treatment modalities of hepatitis B.

Prophylaxis of vertical HBV infections

Małgorzata Pawłowska

The predominant mode of HBV infection in children is vertical transmission. The prevention of HBV vertical transmission is a complex task and includes: in pregnant women with high viral load administration of antivirals in the third trimester of pregnancy and consideration of elective cesarean section and in newborns of all HBV infected women, independently for HBV DNA level, passive-active HBV immunoprophylaxis. Vertical HBV transmission occurs despite immunoprophylaxis in approximately 9-30% of children from mothers with high HBV DNA level. Early identification of HBV DNA status in pregnant women enables the timely administration of antivirals in the third trimester of pregnancy and the consideration of elective cesarean section. Studies on antiviral treatment to prevent perinatal transmission suggest starting treatment in 28-32 weeks to allow an adequate reduction in maternal HBV DNA levels prior to delivery. Among administered drugs lamivudine, telbivudine and tenofovir were examinated. A limitation of both telbivudine and lamivudine therapy is the selection of resistant mutants. Resistance is not observed if tenofovir is given. Elective cesarean section seems to be a method that can help to reduce the incidence of HBV vertical transmission.

Universal screening of pregnant women for HBsAg and passive/active prophylaxis to newborns from HBV-positive mothers is an effective measure through which to prevent vertical transmission.

The road to HBV-elimination from the host, can cccDNA be eradicated?

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Despite of substantial progress in the therapy of chronic hepatitis B (CHB) the complete elimination of hepatitis B virus (HBV) form infected hosts is not reachable at the current status of knowledge. Long-term suppression of HBV-replication is associated with decelerating of disease progression, reversal of liver fibrosis and also partial protection form hepatocellular carcinoma (HCC). Currently available therapeutic means are long-term inhibition of HBV-DNA by HBV polymerase inhibitors and/or immunomodulation by pegylated interferon alpha. Unfortunately the optimal end-point allowing of treatment cessation – HBsAg-loss is still a rare event, especially in HBeAg-negative patients. Furthermore persistent and resistant nature of cccDNA might cause a disease reactivation, even many years after HBsAg-loss and seroconversion. Therefore, the need for further therapeutic options is urgent. Complimentary to HCV and HIV infection small molecules inhibiting other steps of HBV-replication are awaited and at various stages of preclinical/clinical development. The most advanced is entry inhibitor – Myrcludex. Of the various molecules being tested preclinically are HBsAg-inhibitors, HBV nucleocapid assembly inhibitors but also most anticipated cccDNA inhibitors. CccDNA could be either removed by cytolytic or non-cytolytic manner, but also epigenetic control of its activity is possible in cell culture. Those novel classes of anti-HBV molecules include III histone deacetylase inhibitors (HDACi); histone acetyltransferases (HAT) inhibitors; hSirt1 activators; JMJD3 histone demethylase inhibitors. The most exiting results published include lymphtoxin beta receptor (LTbR) agonisation which resulted in over 90% decrease of cccDNA after 30 days of therapy in animal model of HBV.

Occult hepatitis B infections

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Occult hepatitis B infection (OBI) is characterized by the presence of HBV DNA in the absence of detectable HBsAg and it does not include widow period cases. Such infection is usually accompanied by anti-HBc, in some cases by anti-HBs and anti-HBe as well. The clinical relevance of this type of infection is still unclear, however current data indicate that OBI is a risk factor for hepatocellular cancer (HCC). The mechanisms leading to OBI range HBV polymorphism (splicing and mutations resulting from immune pressure), coinfections and the integration of the viral genome. In patients with OBI immunological defects related to IL-12, SDF-1alpha, IgG, C4 and CCR5 expression on immune cells are observed. In Polish blood donors OBI is detected on average in 1/77 436 donation (data from period 2005-2013). In most cases, the concentration of HBV DNA is < 100 IU/ml and is lower in subjects with anti-HBs. Effectiveness of OBI identification depends on the method sensitivity used for HBV DNA detection. Due to the low concentration of HBV DNA. It happens while nucleic acid testing (NAT) to receive discrepant results that are difficult for interpretation. Donors with OBI are older than HBsAg positive, they are infected mainly with genotype D (58%) and A (38%), whereas in HBsAg positive donors dominates genotype A (80%). Infectivity of OBI (50% infectious dose) is lower comparing to HBV window period and while chronic HBsAg positive phase of infection and is estimated for approximately 1000 copies of HBV DNA.

Chronic HBV infection alters monocytes subpopulations and monocytic CD163 expression

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Introduction: Function of monocytes in chronic hepatitis B (CHB) is largely unknown. Classical CD14++CD16– monocytes make-up the majority of blood monocytes, intermediate CD14++CD16+ produce high levels of IL-10, whereas non-classical CD14+CD16++ produce higher levels of TNF-α. This study aims to assess monocytes subpopulations and expression of scavenger receptor CD163 capable of regulatory functions in CHB patients.

Material and methods: 31 patients with HBeAg-negative-CHB and 6 with spontaneously resolved HBV > 20 years earlier (control group) were enrolled. Three patterns of CHB were distinguished: low-replicative carriers (LRC), e-negative-CHB-naïve-to-treatment (ENH) and e-negative-CHB-during nucleos(t)ide analogues therapy with complete HBV-DNA suppression > 24 months (SUP). Subpopulations of peripheral blood monocytes were distinguished by CD14 and CD16 expression. Extracellular membrane expression of CD163 on monocytes was assessed by flow cytometry (BD FACS Calibur).

Results: Ratio of CD14++CD16– cells was different across the groups (ANOVA, $p < 0.02$), with mean frequency of 85.02% in control group, 77.47% in LRC, 76.87% ENH and 75% in SUP groups. Frequency of CD14++CD16+ and CD14+CD16++ monocytes was significantly higher ($p = 0.01$) in CHB patients vs. control (9.53% vs. 4.67% and 10.85% vs. 7.61%). Mean expression of CD163 on CD14 cells was significantly higher in control group (92.98%) vs. CHB ($p < 0.01$) and across CHB groups (LRC = 89.87%, ENH = 88.54%, SUP = 87.89%) ($p < 0.05$).

Conclusions: These preliminary results suggest that persistent exposure to HBV antigens alters monocyte frequency and activation. In CHB significantly higher frequencies of intermediate and non-classical monocytes (responsible for IL-10 and TNF-α) were observed, while classical monocytes were less frequent.

PLENARY SESSION 7
LIVER ENCEPHALOPATHY

Neuropsychiatric assessment in a person with liver encephalopathy

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The liver encephalopathy is associated with various neuropsychiatric disturbances such as affective disorders, sleep disturbances, psychotic symptoms and consciousness disturbances. The chronic liver failure occurs in 50-70% patients. Very important is diagnosis of early stage of encephalopathy (minimal intensity of encephalopathy – MHE), which is connected with developing of overt hepatitis encephalopathy (OHE), associated with higher risk of mortality. Cognitive dysfunctions are detected in many cognitive domains, such as speed of information processing, memory, attention, visuospatial and executive functions. They are related to the brain dysfunctions localized in cortical and subcortical areas, especially in white matter of booth hemispheres particular in frontal cortex, corpus callosum and parietal lobes. These changes may be related to the intensity of the illness.

The neuropsychological assessment should involve the evaluation of patient contact and possible consciousness disturbances and psychotics features, the intensity of affective disturbances – especially depression, which more often show atypical picture, and evaluation of global cognitive abilities and selective dysfunctions. Even though the diagnostic algorithm of cognitive symptoms of liver encephalopathy is not present, the neuropsychological methods may be useful for evaluation of the intensity and character of cognitive dysfunctions, which. For this reason the individual cognitive profile of the patient including pre-illness abilities, education level and age should be perform. In neuropsychological evaluation several tasks from tests batteries (NEUROTEST, CANTAB, Viena Tests Battery) may be applied, in assessment of executive functions – the Wisconsin Card Sorting Test and for evaluation of global cognitive functioning the MOCA and MMSE scales may be implemented.

Minimal hepatic encephalopathy: truly a minimal problem?

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Minimal hepatic encephalopathy (MHE), previously called latent or subclinical comprise the earliest stage of this symptom and is defined by the most recent EASL Guidelines as "the presence of test-dependent or clinical signs of brain dysfunction in patients with chronic liver disease who are not disoriented or display asterixis". The term "minimal" suggests that patients do not express clinical sign of hepatic encephalopathy (HE). However they indeed manifest dysfunction of central nervous system which directly affects concentration, attention or psychomotor abilities. It disturbs patient`s everyday life, including, for example, driving skills such as adaptation to traffic circumstances, maneuvering the vehicle or decision making process on the road. Patients with MHE significantly more commonly take part in traffic accidents. Diagnostic tests for MHE are not different from the ones used in overt encephalopathy and include psychometric tests and more recently a measurement of Critical Flicker Frequency (CFF). The latter permits a pretty precise diagnosis of MHE and is age and education independent. All efforts should be made to make a patient aware of the limitations caused by this symptom. In terms of treatment, there is no single randomized study supporting the use of any particular agents in MHE. It has however been shown that lactulose improves cognitive functions, psychometric hepatic encephalopathy score (PHES) or quality of life in patients with MHE. It may also decrease the risk of road accidents. Prebiotics and probiotics modifications of microbiome as well as rifaximine may also exert positive effects on MHE.

Treatment of hepatic encephalopathy

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Liver encephalopathy is a neuropsychiatric disorder which accompanies acute or chronic liver damage. The central nervous system injury is usually induced by neurotoxic activity of ammonia which disturbs, among others the nervous conduction, and causes the brain oedema. Ammonia, produced in abundant amounts by pathogenic intestinall flora, gets to the systemic circulation, with the exclusion of the liver, due to the portal circulation. Liver encephalopathy treatment should be multidirectional: decrease in ammonia production in the intestines, stimulation of the urea cycle in the liver and in the central nervous system, stimulation of the liver regeneration, the removal of factors inducing liver encephalopathy. The basic therapy is to introduce bisaccharides that are not absorbed from the gastroenteral tract, inhibition of pathogenic intestinal flora by using rifaximine and L-ornityne L-aspargine that decrease ammonia concentration by activation of urea production. Patients with liver cirrhosis require constant monitoring of LE symptoms. When apparent symptoms occur, symptomatic and causative therapy should be introduced and necessary prophylaxis should be considered.

The role of hepatic encephalopathy in children in qualification for liver transplantation

Irena Jankowska

Early symptoms of impaired consciousness in the course of liver damage in children are often absent or nonspecific, especially in the youngest children.

The diagnosis of hepatic encephalopathy (HE) in this group is especially difficult due to the lack of standards and often the lack of cooperation with the patient (e.g. infants). Some authors consider it impossible to determine the degree of encephalopathy in children less than 1-2 years of age.

The etiology of hepatic encephalopathy in children is significantly different than in adults.

Hepatic encephalopathy in infants with acute liver failure occurs most often as a result of infection, inherited metabolic disorders or other reasons (e.g. hemophagocytic syndrome). Rarely, it is a result of poisoning drugs and toxins. Acute toxic liver damage, accompanied by encephalopathy is more common in older children. In recent years, sharp increase in number of teenagers who intentionally overdosed acetaminophen or other drugs has been observed. In older children, the etiology of HE is similar to that in adult patients with hepatic encephalopathy in the course of acute liver failure as a result among other: viral hepatitis, autoimmune hepatitis and Wilson's disease.

The main causes of hepatic encephalopathy in chronic liver failure in young children are still cholestatic disorders, as well as metabolic and genetically determined reasons. In older children HE may occur in the course of autoimmune hepatitis, sclerosing hepatitis or Wilson's disease, but in the era of increasing availability of liver transplantation HE occurs less frequently.

The treatment of HE depends on etiology and childrens age. Some patients are successfully treated due to urgent pharmacological treatment (e.g in the course of tyrosinemia type I) or special elimination diet (e.g. galactosemia). There are also children, who need liver transplantation (LTX) before the onset of irreversible brain damage. Before making the final decision about liver transplantation, a number of pediatric diseases, in which LTx is contraindicated, should be excluded (e.g. primary hemophagocytic syndrome, mitochondrial respiratory chain hepatopathies with multi-organ involvement)

The degree of hepatic encephalopathy is not included in any of the scales used in qualification for LTX, although it is known that at the time of making the decision to transplant it has prognostic significance.

Diagnosis of minimal hepatic encephalopathy (MHE) by Psychometric Hepatic Encephalopathy Score (PHES) or critical flicker frequency (CFF) is associated with liver cirrhosis progression in the follow-up

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Introduction: Psychometric Hepatic Encephalopathy Score (PHES) is regarded as gold standard in diagnosis of MHE but due to lack of standardization in many countries its usefulness is limited. Critical flicker frequency (CFF) is faster and does not require additional experience.

Aim of the study is to assess PHES and CFF in diagnosis of MHE, especially with regard to long-term prognosis.

Material and methods: Fifty patients (mean age 53 yo, 36 male) with liver cirrhosis without overt encephalopathy and 56 healthy volunteers were included. PHES, CFF and ICT tests were performed. All studied subjects had MMSE > 23 and excluded neurological, psychiatric disorders, active alcohol abuse. 21 subjects fulfilled at least 3-month follow-up (range 3-16 months).

Results: The cut-off of < –4 points PHES-score, suggesting MHE was met in 15 patients. Alcohol aetiology (66% vs. 31%, $p < 0.05$) and type-2 diabetes (26% vs. 14%, $p < 0.05$) were more prevalent in MHE. CFF showed moderate sensitivity (50%) and high specificity (80%) in diagnosis of MHE. In the follow-up 67% subjects had an increase of MELD > 2 points. Importantly previous diagnosis of MHE by PHES or CFF showed 100% PPV of disease progression, which means that all patients with abnormal PHES or CFF showed increase of MELD in the follow-up.

Conclusions: Minimal hepatic encephalopathy affects one-third of liver cirrhotics. CFF showed moderate sensitivity and high specificity in diagnosis of MHE. Importantly the diagnosis of MHE either by PHES or CFF was associated with disease progression. CFF due to its simplicity could be used as prognostic tool in liver cirrhosis.

PLENARY SESSION 8
DRUG-INDUCED HEPATOTOXICITY

Severe cholestatic liver injury in a fitness-obsessed white collar

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A 32-year-old male, a lawyer, without significant medical history was admitted to the Department of Infectious Diseases at the J. Gromkowski Voivodeship Specialist Hospital in Wrocław with the symptoms of cholestatic liver injury. He reported the onset of symptoms including yellow skin coloration, urine darkening and malaise, a few days preceding the admission. On being asked multiple times, the patient admitted having taken anabolic steroids of unknown brand in order to increase his muscle mass gain, as gym workout had always been his passion.

The laboratory tests on admission revealed the increased level of liver enzymes (ALT 346 IU/L; AST 109 U/L, Alkaline Phosphatase 152 IU/L and GGTP 36 IU/L), cholesterol assay of 283 mg%, TG level of 250 mg%, total bilirubin level of 9.6 mg% (which increased throughout the hospitalisation up to 26.5 mg/dL). The physical examination revealed significant jaundice with the liver and spleen not exceeding the costal margin. The diagnostic tests excluded hepatotropic viral infection, iron and copper metabolism disorder, autoimmune hepatitis and α_1-antitrypsin deficiency. Due to a very severe pruritus and increasing jaundice, as well as failure to control the symptoms with pharmacological agents (glucocorticosteroids, luminal, anti-histamine agents, cholestyramine) the patient underwent albumin dialysis twice, which led to a transient decrease of bilirubin level and a partial resolution of pruritus. 5 days after the dialysis, the bilirubin level increased again to 23.5 mg/dL. At the same time, pruritus worsened significantly to the extent not observed before. 2 subsequent albumin dialyses were performed which led to relative decrease of bilirubin level and partial resolution of pruritus. The attempt to introduce ursodeoxycholic acid induced another episode of severe pruritus. Eventually, after a 2-month inpatient treatment which led to some clinical improvement due to the use of anti-histamine agent (cetirizine) as well as cholestyramine and glucocorticosteroids, when the laboratory enzyme assays were ALT 124 IU/L, AST 72 IU/L, FA 130 IU/L, GGTP 94 IU/L and bilirubin 8.2 mg/dl, liver biopsy was performed, which revealed toxic, drug-induced liver injury, most likely related to the use of anabolic steroids.

Conclusions: 1. The use of anabolic steroids led not only to the increased muscle mass gain but more importantly it induced cholestatic hepatitis in our patient. 2. Albumin dialysis is effective in resolving pruritus secondary to cholestasis.

Statins and fibrates and hepatotoxicity

Maciej Jabłkowski

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Hepatic dysfunction – Clinical studies of statins have demonstrated a 0.5 to 3.0 percent occurrence of persistent elevations in aminotransferases in patients receiving statins. This has primarily occurred during the first three months of therapy and is dose-dependent. The pattern of more severe hepatotoxicity attributed to statins has included hepatocellular, cholestatic, and autoimmune injury.

In 2012, the US Food and Drug Administration revised its labeling information on statins to only recommend liver function testing prior to initiation of statin therapy and to only repeat such testing for clinical indications. It is agreed that routine monitoring of liver function tests in patients receiving statin therapy is not necessary. Changing medications or lowering the statin dose in patients who are found to have an alanine aminotransferase (ALT) level more than three times the upper limit of normal that is confirmed on a second occasion.

Fibrates: Hepatic effects: Hepatic transaminases can become significantly elevated (dose-related); hepatocellular, chronic active, and cholestatic hepatitis have been reported. Regular monitoring of liver function tests is required; discontinue therapy in patients whose enzyme levels persist above 3 times the upper limit of normal. Hepatic impairment: Contraindicated in patients with active liver disease, including primary biliary cirrhosis and unexplained persistent liver function abnormalities.

Acethaminophen-induced hepatotoxicity

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Acetaminophen-induced hepatotoxicity remains a significant public health concern and common indication for emergent liver transplantation. This problem is largely attributable to acetaminophen combination products frequently prescribed by physicians and other healthcare professionals, with unintentional and chronic overdose accounting for over 50% of cases of acetaminophen-related acute liver failure ALF. Treatment with N-acetylcysteine can effectively reduce progression to ALF if given early after an acute overdose; however, liver transplantation is the only routinely used life-saving therapy once ALF has developed. With the rapid course of acetaminophen-related ALF and limited supply of donor livers, early and accurate diagnosis of patients that will require transplantation for survival is crucial. Efforts in developing novel treatments for acetaminophen-induced ALF are directed toward bridging patients to recovery. This review outlines the most recent developments in diagnosis and management of acetaminophen-induced ALF.

Renal impairment in patients with chronic hepatitis C treated with first generation protease inhibitors

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Introduction: In this single-center study assessment of the incidence, the course, and treatment options for renal impairment (RI) in patients treated with triple therapy (TT) with pegylated interferon, ribavirin and telaprevir/boceprevir (PR/TVR/BOC) were analyzed.

Material and methods: Retrospective analysis included 110 patients with genotype 1b chronic HCV infection aged 18-80 years, who underwent TT with telaprevir (48 patients)/boceprevir (14 patients), or dual therapy (DT) with PR (48 patients). The levels of hemoglobin, serum creatinine concentration (SCr) and estimated glomerular filtration rate (eGFR) were measured at baseline, week 4, 12, 24, 48 of treatment. For the criterion of the diagnosis of renal impairment SCr increase by 1.5 times as compared to the initial values and/or reduction of eGFR by at least 25% of the initial value was adopted.

Results: RI occurred in nine patients (14.5%), eight of whom was treated with TVR and one with BOC. The risk factors associated with RI found in the study were: TT (p = 0.0047), arterial hypertension (p = 0.0036), age (p = 0.0056) and advanced liver fibrosis at baseline (p = 0.002). The medians of the increase in SCr and decrease of eGFR vs. baseline were significantly higher in TT. In the 12th week of observation the median hemoglobin values were significantly lower in TT than in DT group and in the patients with renal impairment in TT group.

Conclusions: RI is a common complication of TT. It is necessary to monitor SCr and eGFR once weekly. RI is often accompanied by anemia. If RI appears ribavirin should be reduced.

POSTER PRESENTATIONS

The abstracts are printed in the form sent by authors, accepted by the Scientific Programme Committee.

Non-alcoholic fatty liver disease and metabolic liver diseases

[1] Association between iron metabolism and nonalcoholic fatty liver disease in children

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Introduction: Association between abnormalities of iron metabolism and nonalcoholic fatty liver disease (NAFLD) has recently been demonstrated in adults.

Aim of the study was to evaluate serum concentration of selected parameters of iron metabolism in obese children with NAFLD.

Material and methods: The study comprised 111 obese children with suspected liver disease (hepatomegaly and/or increased ALT activity and/or liver steatosis in ultrasound). Viral hepatitis, autoimmune and metabolic liver diseases (Wilson's disease, α-1-antitrypsin deficiency, cystic fibrosis) were excluded. Liver steatosis was graded in ultrasound (USG) according to Saverymuttu scale. The total intrahepatic lipid content was assessed by magnetic resonance proton spectroscopy (^{1}HMRS). Serum iron, ferritin, hepcidin levels, total iron-binding capacity (TIBC), soluble transferrin receptor (sTFR) and hemojuvelin (HJV) were also measured.

Results: NAFLD was confirmed in 39 children. Serum ferritin, hepcidin levels and TIBC were significantly higher in children with NAFLD than in obese patients without NAFLD. NAFLD children demonstrate also significantly higher ALT and GGT activities, AST to Platelet Ratio Index (APRI), insulin resistance (HOMA-IR), BMI, waist circumferences and total amount of lipids in ^{1}HMRS. Serum iron, ferritin, hepcidin levels and TIBC demonstrated significant positive correlation with hepatocytes injury expressed trough ALT and GGT activities. Correlation was also demonstrated between APRI and ferritin, hepcidin or TIBC. Moreover TIBC correlated with the degree of liver steatosis in USG.

Conclusions: Association between selected parameters of iron metabolism and hepatocytes injury and APRI in children with NAFLD suggest possible role of iron metabolism in pathogenesis of NAFLD and nonalcoholic steatohepatitis (NASH) progression in children.

[2] The profile of transferrin isoforms in liver diseases

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Aim of the study was to assess the effect of liver diseases on serum profile of transferrin isoforms.

Material and methods: The patients with alcoholic cirrhosis (AC) – 6 subjects, non-alcoholic cirrhosis (NAC) – 6 and toxic hepatitis (HT) – 11 were studied. AC patients were classified according to Child-Pugh scale. The samples were analyzed by capillary electrophoresis on MINICAP electrophoresis system. The normal serum transferrin isoforms are separated into five fractions according to their sialylation level.

Results: There were significant differences in the relative concentrations of trisialo (mean ± SD; 6.42 ± 3.26%) and tetrasialotransferrin (73.25 ± 4.89%) in AC patients when compared to the control group (3.62 ± 1.56%, 76.84 ± 5.62%, respectively) (*U* Mann-Whitney test: $p = 0.002$ for both). The mean concentration of disialotransferrin (10.14 ± 30.14%) were significantly higher in patients with HT in comparison to the control (0.98 ± 1.16%, $p = 0.03$). There were no differences in the concentrations of transferrin isoforms in NAC patients compared to the controls. The levels of tetrasialotransferrin appeared to be different between liver diseases (ANOVA: H = 7.53, $p = 0.02$). Post-hoc analysis revealed that in AC (73.25 ± 4.89%) level of tetrasialotransferrin was lower than in HT (79.44 ± 8.07%, $p = 0.02$). There were significant differences in tetra- and pentasialotransferrin according to Child-Pugh score ($p = 0.003$ and $p = 0.008$). The mean serum tetrasialotransferrin concentration was lower in class C (69.93 ± 2.50%) compared to class B (78.80 ± 4.80%, $p = 0.016$) and A (79.13 ± 2.33%, $p = 0.018$). Pentasialotransferrin level was higher in class C (22.19 ± 3.50%) than in B (17.53 ± 3.20%, $p = 0.025$).

Conclusion: The serum profile of transferrin isoforms shows the alterations in liver diseases, between them and in regard to severity of cirrhosis.

[3] Relationship between of adipokines, lipids and areas under the curve (AUC) of insulin and glucose in children with NAFLD

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Introduction: Insulin resistance (IR) is regarded to be the major complication of obesity leading to liver steatosis and fibrosis.

Aim of the study was to assess IR in children with NAFLD with prolonged glucose challenge test and to look for correlations with other IR markers, adipokines, lipids and liver parametres.

Material and methods: We analyzed metabolic parametres as well as selected endocrine markers in 75 children (64 males and 11 females; aged 13.3 ± 4.11 years) with NAFLD. Prolonged oral-glucose tolerance testing (OGTT) was performer for 240 min.

Results: Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were defined as a fasting plasma glucose (FPG) level ≥ 100 mg/dl, but < 126 mg/dl, and a 2-h post-load glucose on the OGTT of ≥ 140 mg/dl, but < 200 mg/dl respectively. HOMA-IR as a simple indicator of insulin resistance (> 2.5) was increased in 64 pts (mean value 4.89 ± 2.5). We found linear correlation between AUC of glucose and GGTP ($r = 0.33$, $p < 0.02$), leptin ($r = 0.50$, $p < 0.006$), Lp(a) ($r = 0.5$, $p < 0.006$) and fasted glucose. No correlation between ALT and AUCglu and AUCins. Hyperinsulinemia expressed as elevated fasting insulin levels (> 16 mU/l) we observed in 64 children, that is 80%, and impaired glucose tolerance was observed in six children.

Conclusions: HOMA-IR can be used as a screening test of IR, still it seems not to be very specific. Glucose intolerance is not very common when tested with incAUCglu in children with NAFLD but can pick up those with normal fasted glucose levels.

[4] Transient elastography in diagnostic of NAFLD in obese patients – our experience

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Introduction: NAFLD is the world's most common liver disease in adults and children. Transient elastography (TE) – a non-invasive painless method, which measures the stiffness of the liver tissue. With high precision TE confirms or excludes liver cirrhosis. Obesity and overweight are the most significant risk factors for chronic non-infective diseases. Obesity is responsible for almost 100% of cases of fatty liver.

Material and methods: In Bardejov Spa we performe TE on the device Fibroscan 502 touch. Bardejov Spa developed in 2012 a specialized two-week spa stay focused on weight reduction. During this stay clients acquire new knowledge regarding diet, physical activity, are under medical supervision. They also have the opportunity to take the examinations with TE and abdominal ultrasonography.

Results: This spa-stay completed 159 clients (120 women/39 men). The mean BMI in women was 38.4 kg/m^2, in men was 39.9 kg/m^2. We conducted examination TE (in 22 clients the examination could not be performed). In 42 patients (32.6%), we found a significant degree of liver fibrosis (F2 and higher), the presence of cirrhosis was found in 17 clients (10.6%).

Conclusions: NASH is an organ manifestation of metabolic syndrome. TE achieves a high degree of accuracy in the detection of liver fibrosis in patients with chronic liver diseases. TE can be used in monitoring of patients, but also such a screening for liver diseases. Given the current trends and an increase in obesity can be expected that the range of applications of TE will be expanded in the future.

[5] Detection of liver fibrosis in obese children

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Introduction: Obesity is on the 6th position of diseases, which attack the world. In the last years we observe an increase of obesity in children. Liver biopsy was till now the standard diagnostic method for detection of liver fibrosis. Transient elastography (TE) is a noninvasive, painless, standard and safe method which measures the liver stiffness.

Aim of the study was to investigate a degree of liver fibrosis using TE in pediatric obese patients.

Material and methods: In Bardejov Spa we performe TE on the device Fibroscan 502 touch. We use S, M and XL probes.

Results: From 01.2014 to 12.2014 we examined 203 children aged 6-18 years (108 girls, 95 boys). The mean age in girls was 14.3 years, mean age in boys was 13.5 years. Mean BMI in girls was 29.49 kg/m^2, mean BMI in boys was 31.25 kg/m^2. Maximum BMI in children was 43.3 kg/m^2. We find liver fibrosis (F1-F4) in 87 children (42.8%). F1 was observed in 51 children (58.6%), F2 in 16 children (18.4%), F2-F3 in 8 children (9.2%), F3 in 7 children (8%), F3-F4 in 2 children (2.4 %), F4 (liver cirrhosis) in 3 children (3.4%).

Conclusions: Obesity significantly increases morbidity and mortality, impairs quality of life. NAFLD is an integral part of metabolic syndrome. TE can be used in monitoring of patients and such a screening for liver diseases. The cardinal goal for the future is the better diagnostic of NAFLD and multidisciplinary solution of this probleme.

[6] Liver injury in a 6-year-old girl with transfusion-induced iron overload syndrome

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Introduction: Transfusion-induced iron overload syndrome is a commonly observed condition in children receiving regular transfusions due to hereditary anaemia. Since iron excretion mechanisms are not effective the iron is cumulated predominantly in liver but also in other organs and it may lead to liver, cardiac, endocrine, and joint complications. The liver injury is not only characterized by cirrhosis and its complications, but also with an increased risk of hepatocellular carcinoma (HCC).

Case report: 6-year-old girl was admitted to CMHI due to transfusion induced iron overload syndrome. The patient suffered from hereditary haemolytic anaemia of unknown origin. She has been receiving red blood cells transfusions every 4-6 weeks due to refractory low haemoglobin concentrations since the age of 3 months. The elevated activity of transaminases were first observed in 2010 and ultrasound imagine revealed hepatomegaly then. Iron chelation therapy (Exjade) due to elevated ferritin levels has been applied since April 2012. Since the splenectomy was performed in 2013, the patient has not required RBC transfusions, however the liver examination biopsy performed in 2014 revealed liver fibrosis and the presence of iron deposits. Despite fibrosis, liver function was preserved, however elevated activity of transaminases (GOT 64U/l, GPT 155U/l) indicated hepatocytes injury.

Conclusions: The case report indicates that liver involvement should not be underestimated in transfusion-dependent paediatric population. Splenectomy may be considered in patients with severe haemolytic anaemia at earlier stage to prevent them from iron overload induced liver injury.

[7] The frequent PNPLA3 p.I148M polymorphism may modulate the severity of Wilson's disease in paediatric patients

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Introduction: Patatin-like phospholipase domain containing 3 (PNPLA3) polymorphism p.I148M (rs738409) is associated with non-alcoholic fatty liver disease and cirrhosis in chronic liver diseases Wilson's disease (WD) may have a variable course which is not explained by ATP7B mutation. Neurological presentation in children with WD is very rare.

Aim of the study was to evaluate PNPLA3 polymorphism distribution in children with WD with variable clinical presentation.

Material and methods: Clinical and biochemical data was obtained from 44 children with WD diagnosed according to the Ferenci score. In all patients, the PNPLA3 polymorphism was genotyped with a PCR-based assay. We correlated PNPLA3 genotypes with clinical traits of the patients.

Results: In the group of 36 children with WD with hepatitis – 11 patients (30%) had the [IM] genotype and 25 patients (70%) had [II] genotype. Among 5 patients with acute liver failure – 2 patients had [II] genotype (40%), 2 patients – [IM] genotype (40%), and one child – [MM] genotype (20%). Four of them underwent liver transplantation, 1 child died because of multiorgan failure. Two patients had neurological presentation of WD – in all of them [MM] genotype was present. Two patients presented with chronic cirrhosis – all of them had [MM] genotype.

Conclusions: The [MM] genotype of the PNPLA3 p.I148M variant seems to be associated with neurological presentation and cirrhosis in children with Wilson's disease. There is no clear correlation of the acute liver failure with PNPLA3 genotype. Analysis of larger cohorts of patients with WD are urgently needed.

[8] Calculated non-ceruloplasmin-bound copper is not a reliable diagnostic tool in Wilson disease in children

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Introduction: Non-ceruloplasmin-bound (CuNCB) copper concentration is proposed as biochemical diagnostic test in Wilson disease (WD). Its laboratory assessment is very sophistcated and calculated with following formula (CuNCB = Cu total – (3 x ceruloplasmin)) results are used instead. Such a results possibly suffer from the fact that are based on two laboratory measurements and thus have wide confidence intervals. The normal CuNCB concentration is below 15 μg/dl, whereas most patients with WD without therapy have concentrations above 25 μg/dl. There is limited data concerning CuNCB validation as diagnostic test in children.

Aim of the study was to validate the test in a cohort of children with WD.

Material and methods: 62 WD patients diagnosed according to Ferenci score were the study group. 39 patients with liver diseases other than WD were the control group. Discriminant ability and optimal cutoff point were established with ROC curve analysis.

Results: CuNCB concentration concentrations were 6; –2; 26 [median, Q1, Q3] μg/dl and 13; 2; 21 in study and control group respectively. Area under ROC curve was 0.55. The optimal cutoff point was 25 with sensivity 0.26 (0.13; 0.38) and specifity 0.82 (0.66; 0.92). When specifity was outweighed over sensivity the optimal cutoff point was 45 with sensivity 0.05 (0.01; 0.13) and specifity 1 (0.9; 1).

Conclusion: Non-ceruloplasmin-bound copper is not a reliable diagnostic tool in Wilson disease in children although very high (over 45 μg/dl) results are specific for small number of patients.

[9] Early onset of Wilson disease – difficulties in the diagnosis

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The aim of our study was to analyze clinical presentations, diagnostic tests and therapies of early onset Wilson disease < 5 y of age. We retrospectively analyzed data of 130 patients with confirmed diagnosis of WD treated in our center since 1996. 11 patients (5 M, 6 F) had first symptoms or abnormal liver function tests ≤ the age of 5 y, in that group 5 pts. presented with liver dysfunction at the age of ≤ 2 y 4 pts. had family history of Wilson disease. In 3 cases hepatomegaly was observed. The diagnosis of WD was confirmed in 5 cases before the age of 5 y. At baseline the mean ALT level was 279 ± 147 (70-488) and AST level was 156.9 ± 89.6 (48-361). In 9 pts. caeruloplasmin serum level was < 20 mg/dl. Urinary copper excretion was tested in 7 pts. and in 4 pts. the levels were between 50 and 100 mcg/day, only 3 pts. had levels > 100 diagnostic for Wilson disease. Liver copper was tested in 3 pts, all values were higher than 250 μg/gm of dry weight, mean 1187 ± 580.5 (604.5-1766). The most common mutation was p.H1069Q mutation. 7 patients were treated with zinc compounds, in 4 cases penicylamine therapy was started. Bothe therapies were effective. No serious side effects were noticed. Wilson disease can present at early age with significantly increased transaminases and hepatomegaly. Diagnostic approach is challenging as urinary copper excretion is difficult to perform in children ≤ 2 years old and most of all that may not be highly increased.

Surgical treatment of liver diseases

[10] Functional capacity determined in the exercise stress test in candidates for liver transplantation

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Introduction: Functional capacity is considered to be a good predictor of the risk of cardiovascular complications in patients undergoing surgery. However, there is no evidence of MELD score relationship with the functional capacity in the patients referred to liver transplantation (LTx).

Aim of the study was to evaluate the functional capacity determined by metabolic equivalents (METs) and the duration of the exercise (ETD) and their correlation with MELD score in patients qualified for LTx.

Material and methods: We analysed data of exercise test (ET) of 90 (26F) pts with liver cirrhosis, referred to the cardiological assessment for LTx, able to perform the test, aged 48.9 ± 9.34 years, MELD score 13.94 ± 4.57 pts, viral etiology in 49 pts, alcoholic in 23 patients. Additional 23 pts were unable to perform ET. In 69 pts beta-blocker was used.

Results: In 45 (50%) pts the result of ET was inconclusive, in 36 (41.1%) pts negative and in 8 (8.9%) pts positive for exercise induced ischemia. The mean energy expenditure of physical activity was 9.46 ± 2.79 METs and the ETD was 488 ± 175 sec. The MELD score was inversely correlated with METs ($r = -0.34$; $p < 0.01$) and with ETD ($r = -0.24$; $p < 0.01$), however this correlation was weak.

Conclusions: The patients referred for LTx in whom the exercise test was possible, demonstrated good exercise tolerance. The MELD score, despite being negatively correlated with functional capacity parameters, does not seem to be the effective tool to predict the functional capacity in candidates for LTx.

[11] Diagnostic methods in biliary strictures after pediatric liver transplantation

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Introduction: Biliary strictures (BS) are frequent after pediatric liver transplantation (LTx). Clinical presentation may vary from asymptomatic cases with mild laboratory abnormalities toward jaundice and cholangitis.

The main purpose of the study was to analyze the value of diagnostic methods in BS after pediatric LTx.

Material and methods: We performed the retrospective study of 52 children after LTx who developed BS. After LTx all patients were under regular check-up visits. In case of dilatation of bile ducts in ultrasound scan or cholestasis diagnostic evaluation was supplemented by hepatobiliary scintigraphy (HBS) and magnetic resonance cholangiopancreatography (MRCP). If BS was suspected children were referred to percutaneous transhepatic biliary drainage (PTBD), endoscopic retrograde cholangiopancreatography (ERCP) or surgery. Before treatment direct cholangiography confirmed BS in all patients.

Results: Median age at LTx was 9.3 year (0.4-18). Hepatico-jejunal anastomosis was in 27 and duct-to-duct anastomosis in 25 patients. Most BS occurred in the first 12-months after LTx – 32 patients. Median age at diagnosis was 12.9 year (0.5-18). Mean values of laboratory tests at diagnosis were: bilirubin 4.1; GGTP 455 and ALT 123. Sixteen patients presented with normal level of bilirubin and 2 with GGTP below 100. US scan in 88% patients showed dilatation of bile ducts. HBS had 89% sensitivity in detection of biliary obstruction-dilatation of bile ducts in 33 (62%) and impaired biliary excretion in 31 (59%). MRCP was performed in 14 cases and confirmed BS in 100%. Out of 23 liver biopsies 14 (61%) was consistent with impaired bile secretion.

Conclusion: Non-invasive diagnostic methods are highly sensitive in BS diagnosis.

[12] Duodenal-Y-Roux fistula in child with portoenterostomy due to biliary atresia – case report

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Introduction: Kasai hepatoportoenterostomy is a treatment of choice in infants with biliary tract atresia. The bile is drained into the Y-roux intestinal loop and omits duodenum and upper part of jejunum. This is a retrospective analysis of patient's case report.

Case report: We present a girl with biliary atresia treated with hepatoportoenterostomy at the age of 2 months. Patient developed splenomegaly and mild hypersplenism at the age of 1 year. Patient started the endoscopy surveillance for portal hypertension at the age of 2 years (7 endoscopies done within 4 years of observation). The endoscopies showed increasing size of oesophageal varices and presence of deep ulceration of duodenal bulb wall. Patient underwent prophylactic endoscopic band ligation of oesophageal varices and received long term PPI therapy. Duodenal ulcer temporarily healed but reappeared after PPI discontinuation with further formation of small fistula to Y-Roux intestinal loop at the age of 6 years. The fistula allowed for the retrograde bile flow into the duodenal bulb and stomach.

Conclusions: To our knowledge this is the first in the literature report of duodenal-Y-Roux fistula in patient after hepatoportoenterostomy. The presence of the fistula may have a positive effect as it allow the partial bile flow into the duodenum. However with the increase of fistula size the duodenal content may omit upper jejunum what will shorten the alimentary passage and may lead to malabsorption.

[13] Aortic valve replacement in patient with severe aortic regurgitation, qualified for liver transplantation

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Introduction: Liver cirrhosis, may increase perioperative mortality risk of aortic valve replacement (AVR). Delay of AVR until the patient becomes more symptomatic may result in advanced cardiac dysfunction. Successful AVR before liver transplantation (LTx) guarantees a better hemodynamic situation during LTx.

Case report: 46-year-old man with liver cirrhosis (HCV) and suspected hepatocarcinoma, was referred for cardiac assessment before LTx. An year before he was treated for infective endocarditis. On admission he presented no sympotms of heart failure, MELD 13 points. Physical examination revealed loud holodiastolic murmur over the aortic valve area. At transthoracic echocardiography despite the hyperdynamic left ventricle contractility with preserved ejection fraction, severe aortic regurgitation was seen. The destruction of valve leaflets and the perforation of aortic cusp was shown. It was confirmed by transeshophageal echocardiography. Bearing in mind that an excessive load would be on the heart during and after LTx, we adjudged the benefits of AVR outweighed its risk. It was decided to perform the procedure of AVR before LTx. Two weeks later the damaged valve was surgically replaced with a bioprosthesis. The postoperative period was complicated by bloody pericardial effusion treated with pericardial drainage. Five months after cardiac surgery an successful and uneventful LTx was performed. The hemodynamic changes during LTx were well tolerated. The diagnosis of hepatocarcinoma was confirmed in the explanted liver. Ten months after LTx the patient is alive, in good condition.

[14] Hemobilia following liver biosy in children – two case reports

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Introduction: Hemobilia is a rare but severe and potentially fatal complication of liver biopsy. Aim of the study is to present the cases of hemobilia diagnosed at Children's Memorial Health Institute in Warsaw. Two cases of hemobilia were reported after 2500 standard Menghini needle liver biopsies performed over the period of 16 years (1998-2014).

Case 1: 14-year-old girl presented with hematemesis few hours after liver biopsy. USG showed liver hematoma and enlarged gallbladder. Endoscopy showed presence of fresh blood in stomach an duodenum without visible source of bleeding. Scyntigraphy did not show bleeding source. Patient complained on abdominal pain. Hemoglobin concentration decreased and patient required several blood transfusions over the next week. Bilirubin concentration and GGTP activity temporarily increased. The symptoms resolved within two weeks.

Case 2: 16-year-old girl presented with abdominal pain two days after liver biopsy. She was readmitted to the hospital where she presented hematemesis, melena and anemia. Endoscopy showed blood flow from Vater papilla. USG showed markedly enlarged gallbladder filled with bloody fluid. Patient required several blood transfusions and had cholecystectomy due severe abdominal pain and rapidly increasing cholestasis. Symptoms resolved within three weeks.

Conclusions: The risk of hemobilia after standard Menghini needle liver biopsy in our institution is less than 0.1%. Hemobilia is a life threatening event and requires prolonged hospital therapy.

[15] Ileal exclusion in adolescent girl with progressive familial intrahepatic cholestasis (PFIC) – due to a poor quality of life connected with biliary stoma

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Introduction: PFIC is a disorder which should always be suspected in children presenting with pruritus and cholestasis when GGTP activity remains normal. Nowadays partial external biliary diversion (PEBD) is a standard procedure performed on PFIC children not respondent to medical treatment (UDCA). Some children, especially the adolescent patients don't accept the externalstoma for aesthetic reasons.

Clinical case: 13-year-old girl was admitted to our hospital with severe pruritus, short stature and elevated serum bile acids concentration. Based on the patient history and laboratory results, alongside with the liver biopsy result, PFIC was suspected. Molecular analysis confirmed PFIC type 2. UDCA therapy was ineffective and the patient was qualified for the PEBD. 15 years later, due to poor life quality (connected to the presence of a biliary stoma) despite good outcome of PEBD, an alternative surgical procedure, ileal exclusion (IE), was proposed. Just after IE recurrence of pruritus and elevation of bile acids concentration in serum was observed. Treatment with UDCA was started, resulting in a resolution of pruritus and normalization of bile acids concentration. 2 years after IE the patient – continuously treated with the UDCA – has a very good quality of life, without any pruritus and stable bile acids concentration within normal range.

Conclusions: IE may be a good option for older children with PFIC, reaching adulthood, who cannot accept biliary stoma due to the poor quality of life.

HCV

[16] Shear wave elastography as a tool for enrollment of patients with chronic viral hepatitis to therapeutic programs

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Introduction: Shear wave elastography (SWE) is a new tool for non-invasive, quantitative assessment of liver tissue stiffness corresponding to hepatic fibrosis combined with two dimensional, real time, ultrasound imaging, that allow to perform measurement in proper area.

Aim of the study was evaluation of consistence between SWE stiffness and fibrosis in liver biopsy, particularly in respect to differentiation between minimal and advanced fibrosis, which is essential for patients enrollment to NFZ therapeutic programs in Poland.

Material and methods: In 53 patients with chronic hepatitis B or C with available recent liver biopsy reports, hepatic stiffness assessment with SWE (Aixplorer, Supersonic Imagine) was carried out. Results were expressed in kPa and transferred to 0-4 score corresponding to stage of liver fibrosis according to manufacturer calibration. If difference between biopsy and SWE score did not exceed ±1, results were recognized as consistent.

Results: Liver stiffness varied from 4.2 to 34.6 (8.5 ± 0.8) kPa. Consistence between SWE and liver biopsy scores was demonstrated in 46 patients (86.8%) and values demonstrated significant positive correlation ($r = 0.711$). Consistence was 85.7% (12/14) if SWE was carried out within 6 months after liver biopsy and 87.2% (34/39) if time distance between procedures was longer. Among 33 patients with minimal fibrosis in liver biopsy (stage 0-1) only 2 were demonstrated with SWE to have stiffness corresponding to fibrosis stage 2 or more.

Conclusions: Liver stiffness measured with SWE showed good consistence with stage of liver fibrosis, but we still need more patients with advanced liver fibrosis to complete this analysis.

[17] Association between serum endocan and hepatic angiogenesis in chronic hepatitis C

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Introduction: Angiogenesis is a characteristic feature of chronic liver diseases. CD34 is endothelial antigen used to highlight blood vessels density. Endocan (endothelial cell-specific molecule-1) plays a pivotal role in angiogenesis. Since angiogenesis is observed in chronic hepatitis C (CHC), it was taken under consideration if endocan concentration are altered in CHC.

Aim of the study was to assess the number of new blood vessels in hepatic lobules and portal tracts and evaluate relationship between angiogenesis intensity and serum endocan, angiopoietin(Ang)-1 and vascular-endothelial growth factor (VEGF) concentrations in CHC patients.

Material and methods: Circulating markers of angiogenesis were assessed in 74 CHC patients by immunoenzymatic method, whereas CD34 by immunohistochemistry.

Results: CD34 expression in portal tract and lobules was positively associated with fibrosis stage ($r = 0.41$, $p = 0.001$ and $r = 0.55$, $p < 0.001$; respectively). Endocan concentration was significantly higher in CHC patients compared to controls (5.4 ± 2.6 *vs*. 1.0 ± 0.1 pg/ml, $p = 0.01$). Endocan concentration decreased significantly in CHC patients with bridging fibrosis/cirrhosis compared to those with portal/periportal fibrosis (F1 5.7 ± 2.6 vs. F2 5.9 ± 2.4 vs. F3 3.9 ± 1.2 vs. F4 3.3 ± 1.0 pg/ml; F1/2 5.8 ± 2.5 vs. F3/4 3.7 ± 1.1 pg/ml, $p = 0.04$) and in those with more extent steatosis (S0 5.4 ± 2.8 vs. S1 5.9 ± 2.7 vs. S2 2.5 ± 1.3; S0/1 vs. S2, $p = 0.04$). Endocan serum concentration was not associated with CD34 expression, Ang-1 and VEGF levels.

Conclusions: Endocan levels increased in CHC patients with the highest concentration in those with less advanced fibrosis. Decrease in endocan levels indicates bridging fibrosis/cirrhosis and higher steatosis grade. Serum endocan was not associated with the number of neoformed hepatic blood vessels.

[18] Prevalence and risk factors of HCV/HIV co-infection and HCV genotype distribution in North-Eastern Poland

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Introduction: HIV/HCV coinfection predispose to accelerated liver damage and increase of both liver-related and unrelated morbidity and mortality in patients living with HIV.

Aim of the study was to evaluate the prevalence of HCV infection among HIV positive patients treated in Białystok center, along with seropositivity risk factors and genotype evaluation.

Material and methods: Patients with confirmed HIV infection treated in one of 17 HIV/AIDS referral centers in Poland who had HCV serological results available were enrolled. Demographic data, serological and molecular results regarding the HCV and HBV infections were analyzed using Statistica PL software.

Results: Anti-HCV antibodies were detected in 325 out of 457 patients enrolled (71.1%). The highest seroprevalence was found in 30-40 years old group – 81%. The HCV RNA was detected in 195 out of 233 samples tested. The HCV genotype analysis (n = 193) showed genotype 1 predomination – 37.3%, followed by genotypes 3 – 32.1% and 4 – 30.6%. In multivariate regression analysis IVDU way of HIV infection (OD 125.1; 95% CI: 10.75-1453.6), incarceration (OD 4.45; 95% CI: 1.141-17.39) and younger age at the HIV diagnosis (OD 0.857; 95% CI: 0.749-0.981) were identified as risk factors of HCV infection.

Conclusions: HIV/HCV coinfection remains an important medical problem in North-Eastern Poland, requiring relevant attention and preventive and curative actions to be taken.

[19] Visfatin serum concentration and hepatic expression in chronic hepatitis C

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Chronic hepatitis C (CHC) is associated with increased prevalence of steatosis, carbohydrates and lipid metabolism abnormalities. Adipokines may influence inflammatory response and insulin sensitivity, contribute to development of metabolic abnormalities, regulate fibrogenesis, angiogenesis and carcinogenesis. A novel adipokine – visfatin shows immunomodulatory properties, promotes B-cell maturation and enhances activation of leukocytes, synthesis of adhesion molecules and production of proinflammatory cytokines, and exerts insulin-mimetic effects. In a group of 63 non-obese CHC patients (29 M/34 F) infected with hepatitis C virus (HCV) genotype 1b, aged 46.6 ± 14.6 years, BMI 24.8 ± 3.0 kg/m^2, serum visfatin levels and its hepatic gene expression were examined and the subsequent association with metabolic and histopathological features were assessed.

Serum visfatin levels were significantly higher in CHC patients compared to controls (22.7 ± 5.7 vs. 17.8 ± 1.5 ng/ml; $p < 0.001$). Hepatic expression of visfatin was similar in males and females ($p > 0.05$). There was no difference in serum visfatin and its gene hepatic expression regardless of sex, body mass index (BMI), insulin sensitivity and lipids concentrations. There was no mutual correlation between serum visfatin and visfatin hepatic expression.

Visfatin hepatic expression but not visfatin serum levels were higher in patients with steatosis (1.4 ± 0.7 vs. 1.0 ± 0.3; $p = 0.009$ and 21.9 ± 5.3 vs. 24.0 ± 6.0; $p > 0.05$, respectively). There was no difference in serum visfatin and visfatin expression in patients

with various fibrosis stage and inflammatory grade. Serum visfatin levels may reflect its contribution in immunological processes accompanying HCV infection.

Visfatin hepatic expression seems to be a concomitant phenomenon/accelerating factor of liver steatosis in CHC patients.

[20] Efficacy and safety of Parytaprewir/r/Ombitaswir and Dazabuwir with or without Ribavirin in real life therapy of Polish patients with chronic hepatitis C – an interim analysis of AMBER study data

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Introduction: The most recent clinical trials carried out with interferon free regimens in HCV infected patients demonstrated good efficacy and safety profile. We investigated virologic response and safety of early phase treatment with Parytaprewir/r/Ombitaswir and Dazabuwir ± Ribavirin in real life setting in Poland.

Material and methods: Up to now treatment was initiated in 118 patients (61 males, 57 females), aged between 26 and 76 (52.5 ± 12.0 years), 83% PegIFN/RBV experienced, 47% null-responders, 65% with fibrosis F4. They were infected mostly with genotype 1b (85%) with baseline HCV-RNA 1.3 ± 2.0 × 10^6 IU/mL. Treatment was scheduled for 12 weeks (81%) or 24 weeks according to the current label.

Results: In 27 patients HCV-RNA was measured after 1 and 7 days of treatment and was undetectable in 1 and 8 patients respectively, remaining demonstrated mean values reduction by 3 and 4 logs respectively. Week 4 efficacy data were available in 65 patients and HCV RNA was undetectable in 31 (48%) and detectable but unquantifiable in 14 (22%). In remaining 20 patients HCV-RNA decreased by at least 3logs and in 16 was below 100 IU/mL. Among 9 patients who completed therapy 8 have undetectable HCV-RNA and 1 detectable but unquantifiable at the end of treatment (discontinuation in week 11 due to scheduled liver transplantation). Predominant adverse events were fatigue, anemia and jaundice mostly in patients receiving ribavirin.

Conclusions: Available data demonstrate rapid suppression of viral replication on Parytaprewir/r/Ombitaswir and Dazabuwir ± Ribavirin treatment. Minor safety issues seem to be related to ribavirin.

[21] Utility of elastographic method – Fibroscan monitoring for three years in the course of chronic hepatitis C

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Introduction: The non-invasive techniques are routinely used nowadays in diagnosis of cirrhosis and the assessment of treatment efficacy, whereas biopsy is reserved for the uncertain cases.

Material and methods: 55 HCV-infected patients (positive HCV RNA) from the Outpatient Infectious Disease Clinic were enrolled. Each of them had two elastography studies between 2011 and 2014, performed using Fibro Scan M probe, with IQR up to 25%

and the efficacy over 70%. The exlusion criteria included: HIV or HBV co-infection, alcohol abuse, BMI > 30. The results of studies in 23 subjects were eventually analysed.

Results: In our 23 patients, there were 9 women (39%), 14 men (61%), at the age of 26-70 (mean age was 47.1: 49.5 y.o. and 45.7 y.o. in women and men, respectively). The baseline liver fibrosis staging was as follows: F0/1 – 8, F1/2 – 2, F3 – 9 and F4 – 4 patients. Serum ALT levels – 30 to 160 IU/L (mean value of 59.7 IU/L). The follow up FibroScan at 30-36 months gave results: F1 – 10 patients, F2 – 5 patients, F3 – 4 patients and F4 – 4 patients. Liver fibrosis did not progress in 11 (48%) cases (mostly untreated patient – including 6 at Fo-1). It regressed in 8 (30.5%) and progressed in 4 (17%) .

Conclusions: FibroScan elastography is a good diagnostic tool for the evaluation of liver fibrosis severity, monitoring treatment progress in HCV and assessing its efficacy.

HBV

[22] Decreased intrahepatic viral replication but not subviral particles productivity in low replicative patients with chronic HBV infection

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Introduction: HBV remains in the nuclei of hepatocytes as cccDNA even after serological control of the infection. The level and regulation of intrahepatic viral DNA is shifting with the infection phases.

Aim of the study was to analyze hepadnaviral nucleic acids from paraffin-preserved liver biopsies of treatment-naive chronic hepatitis B patients (CHB) in different infection phases.

Material and methods: Methods Viral DNA (including cccDNA) and RNA were quantified from paraffin-preserved liver biopsies of 221 CHB patients by a novel three-in-one (3io) PCR method. Intrahepatic viral parameters of were correlated with serum HBV-DNA and HBsAg levels.

Results: Low replicative (LR) patients had the lowest levels of relaxed circular DNA (rcDNA), pregenomic RNA (pgRNA) and S-gene RNA (S-RNA) but comparable cccDNA levels to other phases. This resulted in the lowest indices for replication but a high HBsAg production ratio (HBsAg/pg RNA) in this phase. cccDNA was negatively correlated with serum HBV DNA in the LR phase while showing no correlation in all other phases. On the other hand, serum HBV DNA correlated with intrahepatic total HBV DNA (r = 0.51), intrahepatic pgRNA (r = 0.51) and S-RNA (r = 0.30) in the liver of all patients.

Conclusions: Diagnosis of low replicative phase requires long-term observation. Individual patients may transit between phases. Intrahepatic hepadnaviral markers may be used as an additional diagnostic tool to support serum-based diagnostics. Despite low replication LR patients have the highest empty surface surplus suggesting that persisting virus can be controlled in terms of its replication but not transcription of S gene.

[23] The prevalence of HBV drug-resistant variants in treatment naïve-patients

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Introduction: Minor drug-resistant variants may pre-exist in every patient infected with HBV. However, there are little data concerning the detection of resistance mutations in patients who have never been treated. Moreover, drug-resistant HBV variants usually occur at low levels.

Aim of the study was to assess the presence of HBV drug-resistant mutants using MALDI-TOF mass spectrometry in the group of treatment-naïve patients.

Material and methods: HBV DNA was extracted from 27 serum samples of chronic HBV (CHB) patients. All patients enrolled for this study have never been treated before with any antiviral drug. The 37 selected HBV variants were analyzed in 4 separate primer extension reactions on the Mass Array (Sequenom) MALDI-TOF genotyping platform.

Results: The analysis was possible for plasma viral loads higher than 17.18 IU/ml. The HBV drug-resistant variants were detected at codons rt80, rt173, rt180, rt181, rt204, rt233, rt236, and rt250. The most common HBV variants were L80I (62%), I233V (81%), M250V (76%), and M204V and – I (68%), of which M204V was the more frequent (60%). Additional HBV variants occurring at one codon were present with an allele frequency of 5%. Only one patient had a single wild-type HBV variant at each of analyzed codons.

Conclusions: This study showed that the pre-existence of natural resistance mutations in treatment-naïve patients is a common feature. Similar observation were made by different groups. However, the frequency of drug resistant variants pre-existence in this study was much higher what definitely was due to the use of much more sensitive detection method.

[24] The presence of HBV cccDNA form in serum and liver biopsy samples of chronically infected patients

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Introduction: HBV genome exists in two different forms: covalently closed circular DNA (cccDNA) and partially double stranded relaxed circular form (rcDNA). There have been some reports that free cccDNA that is normally found in the infected hepatocytes can occur in serum as an early signal of liver damage.

Aim of the study was to investigate the presence of cccDNA in serum and liver biopsy samples of chronically infected patients (CHB).

Material and methods: The study group consisted of 41 patients. Serum and liver biopsy samples were collected at the same time point. HBVDNA was extracted with the use of QIAamp DNA mini kit with changes (carrier DNA was added to the starting material). Next, rolling circle amplification (RCA) was done to amplify cccDNA. RCA products were then digested with SpeI enzyme that cuts only once in HBV genome. Digestion products were analyzed on a 1% agarose gel.

Results: HBV cccDNA was detected in 1 serum and in 25 liver biopsy samples. cccDNA positive serum sample was taken from the naïve patient with the liver biopsy stage and grade 1. HBV serological markers, viral load, hematological variables were not correlated with the presence of cccDNA in liver samples. This form was detected more often in patients with increased ALT level however this wasn't statistically significant.

Conclusions: In this study we demonstrated that cccDNA form may be found in serum samples of CHB patients. However, further investigations are needed to explain the correlation between the serum cccDNA presence and the response to antiviral therapy.

[25] Previous exposure to lamivudine or sequential therapy with lamivudine and entecavir have no impact on virologic response during tenofovir therapy

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Introduction: Tenofovir (TDF) is the first line therapy for chronic hepatitis B. This study presents the results of TDF monotherapy in patients who failed previous nucleoside analogue treatment.

Material and methods: The study included 29 patients treated with TDF 245 mg once daily for 12 months after lamivudine monotherapy (LAM arm; n = 15) or sequential therapy with lamivudine and entecavir (LAM → ETV arm; n = 14). The previous antiviral therapy was discontinued due to lack of efficacy or the presence of resistance mutations to LAM and/or ETV. HBV DNA level was between 2.1–7.27 log 10 IU/ml. 15 patients were HBeAg-positive. 37% had increased ALT activity. Undetectable HBV DNA (< 20 IU/ml) at month 3, 6 and 12 was the primary endpoint while ALT normalisation was secondary endpoints. Control arm included 13 naïve patients received TDF as first therapy.

Results: Primary nonresponse to TDF was not observed. At 3, 6 and 12 months of TDF therapy, HBV DNA was undetectable in 80%, 80% and 80% of LAM arm; 50%, 71%, and 86% of LAM→ETV arm and 54%, 54% and 77% of control arm, respectively. 77% of patients had normal ALT activity at the end of the study.

Conclusions: TDF is an effective antiviral medication in patients with previous exposure to LAM or LAM→ETV. HBV DNA clearance occurred faster in patients in the LAM arm than in the LAM→ETV arm, but the final rates of patient who achieved undetectable HBV DNA and had normal ALT activity in both arms were similar. It was no difference between naïve and treatment experienced patients.

Hepatic encephalopathy and severe liver conditions

[26] Encephalopathy and acute liver failure in patient with epilepsy treated with valproic acid

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Introduction: Mitochondrial cytopathies are a rare group of disorders that are extremely variable in the way people are affected. Epilepsy is a frequent manifestation of mitochondrial disorders. Antiepileptic drug with the most well-known mitochondrial and hepatic toxicity is valproic acid (VA). The aim was to report case of child with epilepsy, treated with VA, who presented symptoms of acute liver failure and encephalopathy.

Case report: 14-years-old girl with drug-resistant epilepsy, treated with topiramat, VA and levetiracetam, was admitted to the local hospital because of unconsciousness. First blood test, CT and NMR scan of brain showed normal results. Then the patient developed partial seizure, coagulopathy (INR 4.66) and the activity of AST (6369 U/l) and ALT (5861 U/l) highly increased. Alcohol, drugs and acetaminophen poisoning were excluded. Patient was transferred to our hospital.

On admission the child was unconscious, with abnormal flexion to painful stimuli and anisocoria. On CT scan massive cerebral oedema. In blood check coagulopathy, abnormal liver test, acidosis and hypoglycemia. In differential diagnosis infections, Wilson disease, alpha-1-antitripsin deficiency were excluded. GCMS and transferrin isoforms were normal. Because of progressing liver damage the child was transplanted.

We suspect mitochondrial cytopathy because of acute liver failure and encephalopathy in patient treated with valproic acid, although no mutations were found in molecular examination-negative result does not exclude mtDNA mutation.

Graft function is normal, but neurological status is still very poor.

Conclusion: In every patient treated with valproic acid with acute liver failure and encephalopathy, mitochondrial cytopathy should be considered as a reason.

[27] Clinical course of the extreme form of cirrhosis in patients with severe cystic fibrosis

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Introduction: Cystic fibrosis (CF) is severe, chronic genetic disorder that affects multiple organ dysfunction. Progressive hepatobiliary fibrosis, portal hypertension infections, diabetes and etc., are important causes of mortality.

Aim of the study: We aimed to present the clinical course of the end stage liver cirrhosis in CF patients with the special highlight of encephalopathy and treatment methods.

Material and methods: This is a retrospective analysis of case records of 4 CF children (aged 17, 17, 15 and 7 years, 2 boy), with many organs dysfunction such as the lung damage, cirrhosis, portal hypertension, diabetes, cachexia, bacterial and fungus infections, a neurological disorder.

Results: Encephalopathy (at one patient symptom was present about 2 years with varying severity, at 2 pts had 2 acute episodes a short periods of time) was the leading manifestation of multiorgan failure in 3 children. All patients received conventional therapy and died before liver transplantation (LTX). One patient with multiorgan failure had encephalopathy triggered by massive oesophageal varices bleeding. This patient received conventional therapy (hemodiafiltration, Rifaximinum, lactulose) and received successful LTX. All signs and symptoms of encephalopathy resolved and one year after transplantation patient's clinical condition and prognosis are satisfactory.

Conclusions: Encephalopathy can be considered as a risk factor for poor prognosis in patients with CF related end stage liver disease and multiorgan failure.

[28] Deterioration of neurological status following penicyllamine therapy in a child with cirrhosis – case report

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Introduction: Wilson's disease (WD) can present with hepatic, neurological or psychiatric symptoms but neurological presentation is very rare in children. Penicyllamine is a standard treatment of WD, but in patient with neurological manifestations it can lead to deterioration of neurological status.

Case report: We report for the first time neurological complications of penicillamine therapy in a patient with primarily liver presentation: a 12-year-old boy who was admitted to our hospital with symptoms of liver cirrhosis – hepatosplenomegaly, limbs oedema and ascites which was accompanied by lab abnormalities – hypoalbuminemia, disturbed coagulation (INR 1.7), thrombocytopenia, hyperbilirubinemia, elevated transaminases. Behavior disorders and problems at school were noticed as well. WD diagnosis was basen on Ferenci criteria which included low ceruloplasmin level (0.09 g/l) and Kayser-Fleischer ring. Penicillamine therapy in increasing doses was started. After 2 months the child developed neurological symptoms such as resting and intension tremor, dysarthria, dysphagia, dystonia, perturbation of facial expression and depression. The brain magnetic resonance imaging revealed typical WD abnormalities. Withdrawal of penicillamine and administration of zinc resulted in no improvement. Finally, because of severe liver damage a combination therapy of zinc and penicillamine was introduced which is continued at the moment. Neurological status slightly improved.

Conclusion: This case report indicates a risk of neurological complications under penicillamine therapy even in patients who do not present clear neurological symptoms, which may require penicillamine withdrawal or a combination therapy with Zinc and close monitoring.

Varia

[29] Liver stiffness measurement for prediction of portal hypertension in children with autoimmune hepatitis

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Introduction: Transient elastography is easily applicable to children with autoimmune hepatitis (AIH). Liver stiffness (LS) measurement strongly correlates to the degree of fibrosis on liver biopsy, liver function tests and inflammation in AIH patients.

Aim of the study was to evaluate the role of LSM as a predictor of portal hypertension in children with AIH.

Material and methods: 30 AIH children (M – 8; F – 22) aged 7-17 years (mean ± SD: 13.7 ± 2.6) were included into the study. LS (E-med) was measured in kPa by FibroScan® (FS). The diagnosis of portal hypertension was based on endoscopy examination showing oesophageal varices, gastric varices or portal gastropathy. Mann-Whitney test was used to compare the results and ROC analysis was done to detect the optimal cut off point for prediction of the portal hypertension.

Results: Portal hypertension was found in 6 (20%) of subjects (oesophageal varices – 6, gastric varices – 3, portal gastropathy – 4). Liver stiffness expressed by E-med in children with portal hypertension was significantly higher than in those without portal hypertension (44.6; 35.3; 65.2 vs. 5; 4.2; 8.8 [median; q1; q3] $p < 0.001$). ROC analysis showed AUC = 0.98 and the E-med optimal cut off point for detection of portal hypertension was greater than or equal 16.6 kPa with sensitivity (95% CI) = 1 (0.54 to 1 [97.5% one-sided CI]) and specificity (95% CI) = 0.92 (0.73 to 0.99).

Conclusion: We demonstrated that LS measurement may be used as a predictor factor for portal hypertension. AIH children with E-med ≤ 16,5 kPa are unlikely to have portal hypertension.

[30] Results of treatment and analysis of prognostic factors in children with biliary atresia

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Introduction: Kasai hepatoportoenterostomy (HPE) and liver transplantation (LTx) dramatically improved prognosis in children with biliary atresia (BA).

Aim of the study was to analyze the risk factors and outcome in children with BA.

Material and methods: We performed the retrospective chart review of 383 children (226 females, 157 males) with BA treated in The Children's Memorial Health Institute between 1984 and 2014. The following parameters were analyzed: age at Kasai operation, age at LTx, anatomical type, bilirubin level before operation, outcome of HPE, co-existence of congenital abnormalities, survival with native liver (SNL), survival after LTx (TS).

Results: HPE was performed at the mean age of 72 days (SD ± 23) and was successful in 187 (49%) patients. The overall 5 and 10 year actuarial survival with native liver was 38% and 29% respectively. Restoration of bile flow was the main indicator of good prognosis. If total bilirubin dropped below 2 mg% within 6 months after HPE the actuarial 5 and 10-year SNL was 70% and 56%. There was no significant correlation between age at HPE and the outcome. Anatomical type of BA, and direct bilirubin level before operation (< 8 mg%) proved to be important predictive parameters. In 116 (33.8%) patients we determined at least one congenital anomaly. BASM abnormalities did not correlate with worse prognosis. LTx was performed in 181 patients with 5-year survival of 92%.

Conclusions: Treatment of BA is surgical with favorable long-term outcomes. Early HPE, but without strict age threshold, and optimal timing of LTx warrant the best results.

[31] Four Polish patients with SRD5A3-CDG

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Introduction: Congenital disorders of glycosylation (CDG) are genetic diseases with an extremely broad spectrum of symptoms. SRD5A3, encoding steroid 5α reductase 3 which takes part in dolichol phosphate biosynthesis, is responsible for a new CDG, SRD5A3-CDG. 15 children and 4 adults with this syndrome have been described so far, mostly Turkish, Baluchi and 3 Polish patients.

Aim of the study was to analyze the typical symptoms of the disease in all Polish patients based on a single center experience.

Material and methods: We reviewed retrospectively 4 Polish children with SRD5A3-CDG, three of whom were earlier described. They have been diagnosed and treated in our Institute since 2000. In all the children isoelectric focusing of serum transferrin and the screening for SRD5A3 mutations were performed.

Results: Two sisters and two urelated boys aged 0.7 (0.3-8) years [median(min-max)] at diagnosis were followed-up for 12.3 (4.5-12.7) y. All patients suffered from psychomotor retardation, muscle hypotonia, visual impairment (optic nerve hypoplasia/atrophy, chorio-retinal coloboma, nystagmus), had elevated liver enzymes, coagulopathy and low levels of LDL cholesterol. In all but one patient craniofacial dysmorphy features were observed. Ichtiosiform skin lesions, cerebellar vermis atrophy in MRI and stereotypic movements were found in two out of four patients. One child was fed by gastrostomy because of malnutrition with improvement, one was obese.

Conclusions: The new SRD5A3-CDG should be considered in patients with combination of delayed psychomotor development, skin lesions, visual impairment and hepatitis with coagulopathy when glycosylation studies are positive. Sequencing of SRD5A3 is required to confirm the diagnosis.

[32] Selected non-invasive markers in diagnostics of liver diseases

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Introduction: The alternative method for liver biopsy may be non-invasive tests.

Aim of the study was to evaluate the effectiveness of some non-invasive scores: Bonacini, King and GUCI for predicting of liver diseases.

Material and methods: Serum samples were obtained from 109 patients with liver diseases: 57 with alcoholic cirrhosis (AC), 30 – non-alcoholic cirrhosis (NAC) and 22 – toxic hepatitis (TH). The severity of liver cirrhosis was evaluated according to the Child-Pugh score. The Bonacini, King and GUCI scores were calculated using specific formulas based on routine laboratory tests and clinical data.

Results: There were significant differences in Bonacini and King scores between liver diseases (H = 32.732, P = 0.000 and H = 6.550, P = 0.0378; respectively), in contrast to GUCI (H = 4.081, P = 0.130). Future analysis showed that the median of Bonacini score was significantly higher in AC (8, range: 2-11) and NAC (7, range: 3-11), than that in TH (4, range: 1-8) ($P < 0.001$ for both comparisons). Also, King score was significantly higher in AC (65.42, 1.50-855.36), than that in TH (20.02, 4.10-266.81) (P = 0.036). All tested scores: Bonacini, King and GUCI appears to vary according to the severity of liver damage (H = 37.033, P = 0.000; H = 30.912, P = 0.000; H = 27.661, P = 0.000; respectively). Post-hoc analysis showed that Bonacini, King and GUCI scores were higher in score C than that in A ($P < 0.001$ for all) and B ($P < 0.001$ for all).

Conclusions: We conclude that both, Bonacini and King scores, differ between liver diseases and the all tested scores, including GUCI, reflect the severity of liver cirrhosis.

[33] Undifferentiated embryonal sarcoma of the liver with extension from inferior vena cava into the right atrium – a case report

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Introduction: Undifferentiated embryonal sarcoma of the liver (UESL) is a third most common malignant hepatic tumor after hepatoblastoma and hepatocellular carcinoma in children. It occurs usually in children 5-10 years of age. Since the introduction of intensive chemotherapy prognosis of children with UESL has improved over the years. The management of these tumors includes chemotherapy and surgical resection. Extension of the tumor via inferior vena (IVC) to right atrium can be observed but is a rare finding in this disease. This can lead to pulmonary embolism and heart failure.

Case report: We report a case of a 6-year-old boy with UELS penetrating through IVC into the right atrium. He was hospitalized of a liver tumor detected on ultrasound examination. Initial symptoms involved a recurrent low-grade fever and abdominal pain. On physical examination, a palpable tumor in the abdomen and systolic and diastolic murmur were found. Computed tomography imaging revealed a tumor in two segments of the right lobe of the liver and a mass within IVC originating from the right hepatic vein and extending into the right atrium. There were no distant metastases. Treatment included: urgent surgical resection of cardiac mass (histologically diagnosed as the UESL) and anticoagulation therapy to reduce the risk of embolisms, chemotherapy according to protocol for childhood high risk sarcoma followed by extendend right hemihepatectomy and adjuvant chemotherapy.

Conclusion: UESL is a malignant tumor which may extent to the heart requiring urgent cardiosurgical intervention and further combined treatment (chemotherapy, surgery of the primary tumor).

[34] Lysosomal eoglycosidases activity in serum and platelet poor plasma parenterally fed patients

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Introduction: Lysosomal exoglycosidases: N-acetyl-β-D-hexosaminidase (HEX), β-galactosidase (GAL), β-glucuronidase (GLU), α-mannosidase (MAN) and α-fucosidases (FUC) are involved in the catabolism of glycoconjugates. It may be expected differences in glycoconjugates metabolism in person fed parenterally reflected by exoglycosidases activity in body fluids.

Aim of the study was evaluation lysosomal exoglycosidases activity in serum and platelet poor plasma obtained from patients fed parenterally.

Material and methods: Concentrations the activity (nmoL/mL/min) of the individual lysosomal exoglycosidase in serum and platelet poor plasma obtained from 7 patients fed parenterally was evaluated by Zwierz *et al.* method, by determination of 4-nitrophenol liberated from 4-nitrophenol derivatives of appropriate sugars.

Results: We found higher concentrations of exoglycosidases activity in the serum than in the platelet poor plasma, collected from the same patient. In all patients, these differences ranged from 18.8 to 21.5% (mean 19.8%).

Conclusion: It seems that better material for testing the activity of lysosomal exoglycosidases is serum than plasma, due to simpler methodology.

[35] Beta-galactosidase in serum and urine of patients fed parenterally

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Introduction: Nutritional therapy refers to clinical and/or biochemical signs of malnutrition or deficiency, where it is a need for timely administration of food for their alignment. Medical procedure concerning parenteral nutrition include assessment of nutritional status and nutritional requirements, as well as clinical monitoring and ensuring the optimal use of the chosen route of feeding. Helpful in this regard may be determination the activity of β-galactosidase (GAL), the exoglycosidase removing galactose from the non-reducing end of the oligosaccharide chains of glycoconjugates.

Aim of the study is to evaluate the activity of GAL in patients fed parenterally.

Material and methods: Blood and urine samples were collected before, after 5 and 10 days of parenteral nutrition, from 23 patients. GAL activity concentration (nmoL/mL/min) was determined by method Zwierz *et al*. Absorbance of released 4-nitrophenol was measured at 405 nm, using the microplate reader ELx800 of BIO-TEK, and computer program KC Junior.

Results: The concentration of GAL activity were significantly lower at 5^{th} (p = 0.043734) and 10^{th} (p = 0.022895) day of parenteral nutrition, as compared to activity before application of parenteral nutrition. Parenteral nutrition significantly reduces the GAL activity concentration in urine at 10^{th} (p = 0.049423), as compared to activity before application of parenteral nutrition.

Conclusions: The GAL activity concentrations in serum and urine may be used in the evaluation status of patients fed parenterally.

[36] Alpha mannosidase in serum and urine of patients fed parenterally

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Introduction: Parenteral nutrition it is practical application of biochemical knowledge in medicine that involves administration all nutrients directly into the circulatory system. Parenterally given nutrients ready to immediate assimilation are necessary for the human body. However, parenteral nutrition may lead to structural and functional changes of various organs, including the liver. Knowledge of the biochemical changes that result from omitting physiological nutritional pathway will give you a chance of proper application and monitoring of nutritional therapy. Of particular interest in this regard is catabolism of glycoconjugates reflected by activity of lysosomal exoglycosidases in serum and urine.

Aim of the study is to evaluate, in patients fed parenterally, the activity of α-mannosidase (MAN), one of the lysosomal exoglycosidases.

Material and methods: Blood and urine samples were collected from 23 persons before, as well as after 5 and 10 days of parenteral nutrition. Activity concentration of MAN (nmoL/mL/min) was evaluated colorimetrically by determination of 4-nitrophenol liberated from 4-nitrofenol-α-mannopiranoside by the method of Zwierz *et al*.

Results: Serum MAN activity concentration was significantly lower after 5^{th} and 10^{th} day of parenteral nutrition, as compared to the MAN activity before starting parenteral nutrition. At 10^{th} day was observed significant increase in serum MAN activity in comparison to 5^{th} day. There were no significant changes in urinary MAN activity during parenteral nutrition.

Conclusions: 1. Parenteral nutrition significantly alters the serum, leaving unchanged urinary MAN activity. 2. Determination serum MAN activity may be useful in monitoring the state of parenterally fed patients.

[37] Blood serum cathepsin D activity of persons fed parenterally

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Introduction: Cathepsin D (CD) (EC 3.4.23.5) is aspartyl-lysosomal peptidase that degrade proteins on several polypetide fragments, than degraded by other endo- and exopeptidases. CD degrades waste cell proteins and activates precursor forms of proteases and inactivates their inhibitors.

Aim of the study was evaluation CD activity in blood serum of persons fed parenterally.

Material and methods: Blood samples were collected from 10 persons: before, after 5 and 10 days of parenteral nutrition. Activity CD (nmoL/mL) was evaluated by the Barret method, using 6% hemoglobin at pH 3.5. Amount of liberated tyrosine was determined by the Folin & Ciocalteau method.

Results: At 5^{th} and 10^{th} day of parenteral feeding there was found tendency to decrease of serum CD activity in comparison to CD activity before parenteral nutrition.

Conclusion: Parenteral nutrition created tendency to decrease serum CD activity that has no application in diagnostics of parenterally fed persons.

[38] 10-years old boy with jaundice and elevated total and unconjugated bilirubin – liver disease or...?

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Introduction: Gilbert's syndrome is a liver metabolism disorder manifested by elevated level of total bilirubin in the bloodstream with the unconjugated bilirubin at most. Finding normal levels of liver enzymes, GGTP and no anomalies in physical examination is helpful with diagnosing a Gilbert's syndrome.

Case report: A 9 years and 4 months old boy was referred to Liver Disease and Liver Transplant Outpatient Clinic because of hyperbilirubinemia and mild anemia. He was observed for Gilbert's syndrome. Perinatal period was intricated by jaundice – treated with phototherapy and exchange transfusion. Physical examination has revealed a slight yellowing of the scleras and skin, without itching and appetite loss. The liver was enlarged about +1 cm, spleen was under a costal arch. The stools were colored. The results of laboratory tests were: Hb 10.6, Ht 32.9, RBC 4.09, WBC 7.6, PLT 242, total bilirubin 2.03, direct bilirubin 0.8, ALAT 11, AspAT 21, GGTP 8. Also infectious (HBV, HCV) and metabolic (α_1-antitrypsin deficiency, Wilson's desease) causes of hyperbilirubinemia were excluded. During next visit USG showed even bigger liver – homogeneous, free of focal lesions – and spleen enlarged to 155 mm length. There were no other significant anomalies found. The molecular test for Gilbert's syndrome showed no mutation. Finally during hematologic consultation the hereditary spherocytosis was diagnosed.

Conclusion: Older children in all cases of hyperbilirubinemia should be widely diagnosed for most common causes of it, including haemolytic ones.

[39] Sever liver injury in a 16-year-old girl with hereditary spherocytosis

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Introduction: Hereditary spherocytosis (HS) is the most common inherited hemolytic anemia. Clinical symptoms of HS in children are usually: anemia, hyperbilirubinemia, splenomegaly, and increased risk of developing gallstones. Repeated transfusions may lead to hemosiderosis, but hepatic fibrosis and liver insufficiency rather occur in older patients with hemolytic anemias.

Case report: We present a case report of 16-year-old girl with HS and signs of liver decompensation with ascites and portal hypertension. She was referred to the CMHI with suspicion of a portal vein thrombosis. Due to aplastic and hemolytic crisis multiple red blood cells transfusions were performed. Physical examination showed jaundice, splenomegaly, ascites, and limbs oedema. Laboratory findings revealed anemia and liver function impairment. Ultrasound imaging not only excluded portal vein thrombosis but also revealed hepatosplenomegaly and features of portal hypertension. In the course of diagnosis infectious and metabolic etiologies were excluded. Elevated immunoglobulin G levels and positive ASMA and ANA antibodies indicated autoimmune reaction. Due to refractory anemias, splenectomy and surgical liver biopsy were performed in 2014 and patient was qualified to liver transplantation. Examination of liver histology revealed features of liver cirrhosis without any signs of interface hepatitis. After splenectomy the jaundice significantly resolved and the patient condition stabilized.

Conclusions: The case report underlines complications of RBC transfusions and their impact on livers function. It seems reasonable to consider splenectomy since the condition increases the risk of all kinds of liver injury from cholelithiasis to sever hepatic impairment with liver decompensation.

[40] Cholestasis in a child with Kawasaki disease. A case report

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Introduction: Patients with Kawasaki disease (KD) may have a hepatobiliary manifestation ranging from asymptomatic increase in liver enzymes to severe cholestatic hepatitis and/or acute acalculous cholecystitis (AAC). Gallbladder abnormalities are observed with up to 15% of patients during the first few weeks of illness. The etiology of liver involvement for patients with KD is still not clear and probably multifactorial.

Case report: We present a case report of 7-year-old boy with cholestasis in course of KD. From the beginning of the KD the boy suffered from abdominal pain and constipation. The patient was treated with intravenous immunoglobulin (IVIG) and 6 weeks later he presented cholestasis with increased levels of liver enzymes. The ursodeoxycholic acid therapy was implemented. Because of the abdominal pain with cholestasis the MRI was performed and revealed hepatomegaly, splenomegaly, enlargement of the pancreas, the hydrops of gallbladder and the dilatation of the bile ducts. Because of persistent jaundice and itching patient was transferred to CMHI. Rifampicin was added to the therapy. The endoscopic retrograde cholangiopancreatography with sphincterotomy was performed. During the follow up the cholestasis subside and control ultrasound one year later reveled normal liver with undiluted gallbladder and bile ducts.

Conclusion: Cholestasis and AAC in course of KD is generally benign but some cases may require medical, endoscopic or surgical therapy.

[41] Acute on chronic hepatitis. A case report of AIH/PSC/colitis overlap syndrome in a 15-year-old boy

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Introduction: Acute on chronic liver failure (ACLF) is a disease in which there is a rapid deterioration of liver function in patients with chronic liver disease, which is usually associated with a precipitating event. It is characterized by increased mortality due to multiple organ failure.

Case report: We present a case of a boy with AIH/PSC overlap syndrome and colitis, after one episode of variceal bleeding, in whom liver function was stable for 4.5 years of treatment. At 15 years of age, the patient was hospitalized due to deterioration of general condition, severe abdominal pain, diarrhea, vomiting and weight loss. There was also a rapid deterioration of liver function (increased bilirubin, coagulation disorders) and deterioration of renal function. Wide spectrum diagnostics were performed, including endoscopy and identifying an infectious agent, which did not aide in determining the cause of the symptoms.

After 2 months of hospitalization, there were two episodes of massive bleeding from the gastrointestinal tract. The patient was transferred to the Intensive Care Unit. After initial stabilization of his general condition, liver transplantation was performed.

Conclusion: ACLF can cause liver failure and the need for its transplantation.

[42] Gastrointestinal symptoms in Kawasaki disease – review of the literature

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Introduction: Kawasaki disease (KD) is a systematic vasculitis of children that affects small- and medium-sized arteries with predilection to coronary arteries. The diagnostic criteria for KD are fever lasting at least five days and four of the five following conditions: cervical lymphadenopathy, polymorphous exanthema, nonpurulent conjunctivitis, changes in the lips or oral mucosa, changes in extremities. Although gastrointestinal (GI) involvement does not belong to the classic diagnostic criteria, abdominal pain, liver function impairment or gallbladder hydrops are observed in some patients with KD.

Review of the literature: We searched Medline to identify original articles that described GI abnormalities observed in patients with KD. The most common GI symptoms of KD reported in identified studies was abdominal pain, however vomiting, diarrhea and jaundice were also observed. Hepatoegaly, but not splenomegaly was detected in children with KD in physical examination. In laboratory findings elevated alanine aminotransferase and gamma-glutamyl transpeptidase were noted in almost all patients with abdominal pain and in few cases was associated with conjugated hyperbilirubinemia. Gallbladder hydrops was common abnormality found by ultrasound. Gallbladder abnormality can be associated with resistance to intravenous immunoglobulin – typical treatment for KD. The prognosis in KD depends mainly on cardiac complications. In almost all cases the resolution of GI symptoms and laboratory abnormalities was observed.

Conclusions: Gastrointestinal symptoms can be the initial presentation masking typical symptoms of KD. The difficulty in diagnosing KD with atypical manifestation can lead to delay in appropriate treatment increasing the risk for complications, especially coronary artery abnormalities.