Influence of pancreatic steatosis severity on the course of pediatric nonalcoholic fatty pancreas disease

Abstract. Background. Nonalcoholic fatty pancreas disease is an excessive fat infiltration of the pancreas due to obesity in the absence of secondary steatosis. Nonalcoholic liver disease is associated with progressive course; whether presence and progression of nonalcoholic fatty pancreas disease is accompanied by specific structural and laboratory findings, it still remains unclear. Objective: to establish the features of sonological and laboratory findings in children with nonalcoholic fatty pancreas disease depending on steatosis degree. Materials and methods. We observed 93 children aged 7 to 17 years, the average age was 11.87 ± 2.82 years. Degree of pancreatic steatosis was evaluated by ultrasonography. In order to determine pancreatic fibrosis and steatosis, shear wave elastography and steatometry (quantitative estimation of the ultrasound attenuation with determination of average ultrasound attenuation coefficient (UAC)) were performed using Ultima PA Expert apparatus (Radmir, Ukraine). Liver fibrosis and steatosis were diagnosed with the usage of FibroScan 502 Touch (France) with controlled attenuation parameter (CAP) function. Depending on the presence of pancreatic steatosis, children were divided into the following groups: group 1 — 50 patients with pancreatic steatosis and obesity/overweight; this group was divided into subgroups: S1 — 20 individuals with degree 1 pancreatic steatosis, S2 — 22 children with degree 2 pancreatic steatosis, S3 — 8 subjects with degree 3 pancreatic steatosis; group 2 — 30 patients without pancreatic steatosis with obesity/overweight, group 3(control) — 13 children with normal weight. All patients and their parents had given their agreement to participate in the study. We provided blood count with determination of erythrocyte sedimentation rate (ESR), liver function test (alanin aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGTP) and test for serum amylase level. Insulin level was determined by immunoassay with calculation of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Statistical analysis was performed using Statistica 7.0 software by one-way analysis of variance followed by post hoc analysis. Results. Children with degree 3 pancreatic steatosis compared to group 3 demonstrated higher level of ESR — by 1.86 times (p = 0.01), ALT — by 1.86 times (p = 0.006), AST — by 1.96 times (p = 0.00019), GGTP — by 2.10 times (p = 0.0001). We found that patients with pancreatic steatosis had higher level of insulin vs control group (S1 subgroup — 18.38 ± 5.07 μU/ml; S2 — 30.76 ± 3.92 μU/ml; S3 — 33.70 ± 5.37 μU/ml; group 2 — 18.70 ± 2.98 μU/ml; group 3 — 9.480 ± 5.067 μU/ml (p = 0.00262)). Also, patients with pancreatic steatosis demonstrated higher level of HOMA-IR compared to the control group (S1 — 4.04 ± 0.87; S2 — 7.11 ± 0.96; S3 — 7.99 ± 1.35; group 2 — 3.81 ± 0.73; group 3 — 1.94 ± 0.92 (p = 0.00156)). CAP level increased in patients with pancreatic steatosis (S1 subgroup — 234.50 ± 9.94 dB/m; S2 — 239.05 ± 8.99 dB/m; S3 — 245.33 ± 17.21 dB/m; group 2 — 197.87 ± 7.70 dB/m; group 3 — 172.754 ± 12.170 dB/m (p = 0.00001)). UAC had maximal level in children of S3 subgroup (S1 — 2.55 ± 0.08 dB/cm; S2 — 2.56 ± 0.09 dB/cm; S3 — 2.74 ± 0.14 dB/cm; group 2 — 2.26 ± 0.08 dB/cm; group 3 — 1.72 ± 0.15 dB/cm (p = 0.00001)). Patients with pancreatic steatosis had higher level of liver and pancreatic stiffness, but significance of difference was low (p = 0.59). Conclusions. Pediatric nonalcoholic fatty pancreas disease was accompanied by liver steatosis, higher level of inflammation markers and insulin resistance that increased with growth of steatosis degree. Keywords: nonalcoholic fatty pancreas disease; nonalcoholic fatty liver disease; steatometry; elastometry; children
Increased level of triglycerides and free fatty acids can cause ectopic fat deposition in such organs as liver, heart, muscles, biliary tract and pancreas [1]. The excess fat in these organs can contribute to proinflammatory condition with metabolic consequences and development of chronic disease. One of the most significant complications of obesity is insulin resistance, which is also closely related to metabolic syndrome, type 2 diabetes mellitus, increased cardiovascular disease risk and liver steatosis and steatohepatitis [2].

Nonalcoholic fatty pancreas disease (NAFPD) is an excessive fat infiltration of the pancreas due to obesity in the absence of secondary steatosis [1, 2]. Fatty pancreas is a common ultrasound finding which is characterized by increased echogenicity in comparison to the normal pancreas [3].

The main risk factors for the development of NAFPD are obesity, insulin resistance and advanced age, which are the same with nonalcoholic fatty liver disease (NAFLD). Therefore, both NAFLD and NAFPD potentially may have the metabolic consequences [2]. It is known that progression of NAFLD is accompanied by steatohepatitis with possible development of fibrosis, advanced insulin resistance and high cardiovascular risk [2, 3]. Whether the severity of pancreatic steatosis influences the level of inflammation of the pancreatic parenchyma, its exocrine and endocrine function or does not, it’s still unclear.

The aim of the study was to establish the features of sonological and laboratory findings in children with non-alcoholic fatty pancreas disease according to steatosis degree.

Materials and methods

Patients

The study included 93 children aged 7 to 17 years, average age was 11.87 ± 2.82 years. According to the presence of pancreatic steatosis children were divided into the following groups:

— group 1 — 50 patients with pancreatic steatosis and obesity/overweight. This group was divided into subgroups: S1 — 20 children with degree 1 pancreatic steatosis, S2 — 22 subjects with degree 2 pancreatic steatosis, S3 — 8 patients with degree 3 pancreatic steatosis;
— group 2 — 30 obese/overweight children without pancreatic steatosis;
— group 3 (control) — 13 individuals with normal weight.

There were no significant gender differences — 43.1% of patients were girls and 55.9% were boys. All children and their parents had given their agreement to participate in the study.

Clinical and biochemical parameters

The assessment of trophic status was carried out according to body mass index (BMI) Z-score depending on the age and sex proposed by World Health Organization [4]. We made measurement of the waist circumference (WC) and compared obtained values with the data of the percentile tables [5], hip circumference (HC) with calculation of WC/HC ratio. The blood samples were received after an overnight 12-h fasting. Such examinations as complete blood count with erythrocyte sedimentation rate (ESR) determination and liver function test were conducted on StatFax 1904 Plus (Awareness Technology, USA). The concentration of insulin was measured using the immunoassay by StatFax 303 Plus (USA).

Ultrasound study

Ultrasound examination of the abdominal cavity was performed according to the generally accepted technique with usage of Toshiba Xario (Japan). The presence of pancreatic steatosis and its degree were determined using the technique proposed by J.S. Lee et al. (2009) [1, 6]. Pancreatic steatosis was diagnosed in case of increased echogenicity of the pancreas in comparison to echogenicity of the kidney.

Elastometry and steatometry (estimation of ultrasound attenuation coefficient (UAC)) were performed on Ultima PA Expert® (Radmir, Ukraine). Study was carried out to obtain recurrent values of stiffness and UAC; 5 measurements were performed in each part with determination of mean value.

To evaluate liver fibrosis and steatosis, we performed transient elastography using FibroScan 502 Touch (France) with determination of controlled attenuation parameter (CAP).

Fat distribution was evaluated using the ultrasound scanner Toshiba Xario SSA660-A (Japan). The following parameters were evaluated based on the average arithmetic values of three measurements: subcutaneous fat (SF), preperitoneal fat (PPF) with abdominal wall fat index (AFI) calculation according to formula [6]:

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AFI = \frac{PPF_{\text{max}}}{SF_{\text{min}}}.\]

Statistical analysis

For statistical analysis, we used the Statistica 7.0 software. The analysis of variance was used to compare the five groups by the severity of fatty pancreas; post hoc tests were applied to detect subgroup differences. Correlation analysis was performed using the Spearman’s rank correlation coefficient. A value of p < 0.05 was considered statistically significant.

Results

Clinical and biochemical parameters

When analyzing anthropometric data, we found that with the growth of pancreatic steatosis degree, BMI and WC percentile also increased. However, level of BMI Z-score didn’t significantly differ (Table 1).

It was found that the degree of pancreatic steatosis positively correlated with waist to hip ratio (r = 0.54, p < 0.05). Patients from groups 2, 3 and S1, S2 subgroups didn’t differ by gender, but we found that 75% of S3 subgroup patients were male. Patients didn’t differ by the age.
When analyzing the data of the blood count, we found that the level of ESR was higher in children with pancreatic steatosis. The average level of ESR in children of S2 subgroup twice exceeded the level of ESR in children with normal weight (p = 0.0009), also we found a positive correlation between the degree of steatosis and ESR level (r = 0.32, p < 0.05) (Table 2).

The level of leukocytes showed a tendency to be increased in children with pancreatic steatosis, so in the S3 subgroup the average level of leukocytes was 7.08 G/l, in children with a normal weight — 5.38 G/l (p = 0.058) (Table 2). Other parameters of the blood count didn’t differ significantly between groups.

Regarding liver function tests, the level of γ-glutamyl transpeptidase (GGTP) and aspartate aminotransferase (AST) positively correlated with the degree of steatosis: in the S3 subgroup, the mean alanine aminotransferase (ALT) level was 1.86 times higher than in group 3, and the GGTP level — 2 times, respectively (p < 0.05). The level of blood amylase in children of the S2 subgroup was significantly lower than in the control group (p < 0.05).

We found that the level of insulin (r = 0.39, p < 0.05) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (r = 0.46, p < 0.05) positively correlated with the degree of steatosis, gradually increased with increasing of steatosis degree (Fig. 1). The average level of insulin in the S3 subgroup was 33.70 ± 5.30 µU/ml, HOMA-IR — 7.99 ± 1.35 that was significantly higher compared to the corresponding control group parameters.
Ultrasound study

When analyzing data of abdominal fat index, we found that its level increased with steatosis degree growth (p = 0.056) (Fig. 2). We found that pancreatic UAC level increased according to the degree of steatosis and was significantly higher in patients with steatosis as compared to the children without steatosis (p < 0.05) (Fig. 3a). The level of CAP also increased with the growth of pancreatic fat level (Fig. 3b). The degree of pancreatic steatosis positively correlated with pancreatic UAC (r = 0.53, p < 0.05) and CAP (r = 0.46, p < 0.05).

During the analysis of elastography data, no reliable difference was established between the groups (Table 3), but we found a negative correlation between the pancreatic stiffness and pancreatic UAC (r = –0.29, p < 0.05).

We also evaluated positive correlation between UAC and CAP (r = 0.28, p < 0.05).

The liver steatosis was diagnosed in 55.0% of children in S1 subgroup, in S2 — in 54.5%, in S3 — in 62.5% and in group 2 it amounted 16.75%. Liver stiffness according to FibroScan didn’t significantly differ (Table 3).

Discussion

Correlation between AFI, WC/HC ratio and pancreatic steatosis showed that degree of the latter depends on visceral fat distribution. Our findings confirm that abdominal obesity plays an important role in the development of pancreatic steatosis. Progression of central obesity was followed by increasing severity of pancreatic steatosis.

Such inflammation signs as growth of ESR and leukocytes level depending on steatosis degree can be explained by chronic inflammation that accompanies ectopic fat accumulation. Notably, chronic inflammation is capable of inducing insulin resistance, lipolysis, and interstitial fibrosis in adipose tissue [7].

Likewise, we found that the growth of pancreatic steatosis degree is associated with insulin resistance. This data confirms previous study of J.S. Lee et al. (2009) [1]. However, in this study after adjusting for factors related to body fat distribution, particularly visceral fat, the strong association with insulin resistance disappeared. Authors suggest that visceral fat is a much stronger relational factor that influenced the relationship between fatty pancreas and insulin resistance.

In our study, in a majority of cases pancreatic and liver steatosis were found simultaneously, and most fatty liver patients (83.25%) also showed fatty pancreas. This
implies that fatty pancreas could be used as the initial indicator of ectopic fat deposition and as an early marker of insulin resistance, which is a key element of fatty liver and/or metabolic syndrome [1, 6].

Increased ALT and GGTP levels can be explained by coexistent liver steatosis and similarly by association of these parameters with pancreatic function. We observed increased level of liver enzymes only in patients of S3 subgroup that confirms negative effect of pancreatic steatosis progression. Study of Li Wang et al. provided the possibility of using elevated liver enzymes as simple biomarkers of early insulin secretion deficit in type 2 diabetes, especially in young obese patients. It has been suggested that elevation of liver enzymes including ALT, AST, and GGTP may be associated with insulin resistance. The relationship between liver enzymes and islet β-cell function might be based on oxidative stress existing in liver fat infiltration, since the obesity in adolescents is always accompanied by fatty liver of different severity. Several studies showed that cellular GGTP level is closely related to oxidative stress indicators in vivo [7–9].

Therefore, even though we did not have the direct evidence of pancreatic fat infiltration in our study, we also think that oxidative stress exists both in liver and pancreas in case of steatosis.

In study of N.S. Patel, pancreatic fat content was lower in NAFLD patients who had advanced fibrosis [10]. These findings suggest that fat accumulation in patients with NAFLD probably also occurs in other organs including the pancreas as shown in this pilot study. Our study has found the association of pancreatic steatosis with pancreatic and liver stiffness, but we also found a negative correlation between pancreatic attenuation parameter and pancreatic stiffness. We noted a tendency to decreased pancreatic stiffness in subgroup S1 comparing with control group. In addition to this fact, a tendency to growth of pancreatic stiffness in S3 subgroup as compared to the control group suggest that early stage of pancreatic steatosis is associated with decreased stiffness, which rises according to steatosis degree, probably, due to development of inflammation.

Decreased amylase in S2 subgroup compared to control also can be explained by changes in pancreatic parenchyma. It is known that fatty pancreas may lead to exocrine-endocrine dysfunction and to the loss of β-cell mass and function, which may cause the decrease of serum amylase [10]. Relative growth of amylase in S3 subgroup comparing to S2 subgroup can be explained by development of parenchymal parenchyma inflammation (steatopancreatitis) in case of steatosis progression. Wu et al. found that serum amylase values were significantly lower for the fatty pancreas as compared to normal pancreas [12]. Lee et al. also found that low serum amylase levels were associated with an increased prevalence of metabolic syndrome [1]. Studies of Nakajima et al. [14] showed that low serum amylase levels may be associated with NAFLD and metabolic syndrome through insulin resistance and fatty pancreas. However, according to Jinmei Yao relative serum amylase increase may be an independent factor of more advanced hepatic fibrosis [11, 13].

Our study showed that growth of pancreatic steatosis level is accompanied by increased visceral fat, insulin resistance, growth of liver enzymes and relatively decreased serum amylase. Pancreatic steatosis level was associated with such sonological parameters as ultrasound attenuation of the pancreas and liver.

Conclusions

1. Fatty pancreas is associated with central obesity, chronic inflammation and insulin resistance increasing with growth of pancreatic steatosis degree.

2. Pancreatic steatosis can proceed concurrently with liver steatosis and may be accompanied by growth of liver enzymes according to degree of pancreatic steatosis.

3. Development of pancreatic steatosis was followed by reduction of exocrine function in early stages of steatosis, with its relative growth in case of advanced steatosis, possibly due to development of steatopancreatitis.

4. Sonologically diagnosed fatty pancreas isn’t metabolically inert, and pediatrics should pay attention to it.

5. Implementation of steatometry can improve diagnosis of pancreatic steatosis and its level.

References


Вплив тяжкості стеатозу підшлункової залози на перебіг неалкогольної жирової хвороби підшлункової залози в дітей

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Використання динамічної еластографії та стеатометрії в діагності неалкогольної жирової хвороби підшлункової залози дозволяє визначити особливості цих процесів, а також зосередитися на впливах тяжкості стеатозу підшлункової залози на перебіг неалкогольної жирової хвороби підшлункової залози у дітей.

Цель:

Визначення впливу тяжкості стеатозу підшлункової залози на перебіг неалкогольної жирової хвороби підшлункової залози у дітей.

Пациенти та методи:

Ми спостерігали 93 дітей віком від 7 до 17 років, середній вік 11,87 ± 2,82 року. Степень стеатозу підшлункової залози оцінювали за допомогою ультразвукографії. Пациентам проводили звуковивихильну еластографію і стеатометрію. Кількість відчуття стеатозу залежно від ступеня стеатозу була залучена для визначення середнього коефіцієнта загасання ультразвуку з визначенням середнього коефіцієнта загасання ультразвуку (КЗУ) підшлункової залози за допомогою апарату Ultima PA Expert («Радмір», Україна). Фіброз та стеатоз підшлункової залози були діагностовані з використанням апарату FibroScan 502 Touch (Франція) з функцією контролюваного параметра ультразвукового загасання (КПУЗ). Діти були розділені на наступні групи: 1-ша група — 50 пацієнтів зі стеатозом підшлункової залози і ожирінням; 2-та група — 30 пацієнтів без стеатозу підшлункової залози з ожирінням; 3-тя група — 9 дітей із надмірною вагою, 3-тя (контрольна) група — 13 дітей із нормальною вагою. Пацієнтам були проведені загальноферментний аналіз з розрахунком індексу інсулінорезистентності НОМА. Статистичний аналіз проводився з використанням програмного забезпечення Statistica 7.0 за допомогою дисперсійного аналізу (ANOVA) з наступним post hoc аналізом. Результати. У дітей групи S3 порівняно з контрольною групою продемонстровано більш високий рівень ШОЕ — в 1,86 раза (р = 0,006), АСТ — в 1,96 (р = 0,00019), ГГТП — в 2,10 раза (р = 0,0001). Ми виявили, що пацієнти зі стеатозом підшлункової залози мали більш високий рівень інсульну порівняно з контрольною групою (підгрупа S1 — 18,38 ± 5,07 мкОд/мл, S2 — 30,76 ± 3,92 мкОд/мл, S3 — 33,70 ± 5,37 мкОд/мл; 2-га група — 18,70 ± 2,98 мкОд/мл; 3-тя група — 9,480 ± 2,98 мкОд/мл (р = 0,00262)). Також у пацієнтів зі стеатозом підшлункової залози відмічено більш високий індекс НОМА порівняно з контрольною групою (підгрупа S1 — 4,94 ± 0,87, S2 — 7,11 ± 0,96, S3 — 7,99 ± 1,35; 2-га група — 3,81 ± 0,73; 3-тя група — 1,94 ± 0,92 (р = 0,00156)). КПУЗ був підвищеним у дітей зі стеатозом підшлункової залози порівняно з контрольною групою (підгрупа S1 — 234,50 ± 9,49 дБ/м, S2 — 239,05 ± 8,99 дБ/м; S3 — 245,33 ± 17,21 дБ/м; 2-га група — 197,87 ± 7,70 дБ/м; 3-тя група — 172,754 ± 12,17 дБ/м (р = 0,00156)). КЗУ збільшувала максимальних рівнів у дітей підгрупи S3 (S1 — 2,55 ± 0,08 дБ/см, S2 — 2,56 ± 0,09 дБ/см, S3 — 2,74 ± 0,14 дБ/см; 2-та група — 2,26 ± 0,08 дБ/см; 3-тя група — 1,72 ± 0,15 дБ/см (р = 0,00001)). Пацієнти зі стеатозом підшлункової залози мали вищий рівень жорсткості печінки та підшлункової залози, проте значущість відмінностей була недостатньою. Констатуючи результати, показало, що неалкогольна жирова хвороба підшлункової залози в дітей супроводжується стеатозом печінки, зростанням рівня маркерів запалення та інсулінорезистентності, що збільшуються при зростанні ступеня стеатозу.

Ключові слова: неалкогольна жирова хвороба, стеатоз підшлункової залози, сонографія, стеатометрія, еластографія.
Матеріали і методи. Ми навбачали 93 дитин в віці від 7 до 17 років, середній вік 11,87 ± 2,82 роки. Степень стеатозу поджелудочного жовчного міхура оцінювали з допомогою ультрасонографії. Пациєнтам проводилось едінокільцева еластографія і стеатометрія (колівково-кільцева оцінка потужності ультразвуку). Еластографія проводилась за допомогою апарату Ultima PA Expert («Радмир», Україна). Фіброз і стеатоз печінки були діагностовані за допомогою апарату FibroScan 502 Touch (Франція) з допомогою контролюваного параметра ультразвукового затухання (КПУЗ). Діти були розподілені на наступні групи: 1-га група — 50 пацієнтів з стеатозом поджелудочного жовчного міхура і ожирінням/переважним вагом; 2-та група — 30 пацієнтів без стеатозу поджелудочного жовчного міхура і ожирінням/переважним вагом; 3-та (контрольна) група — 13 дітей з нормальним вагом. Пацієнтам були проведено об'єктивний аналіз крові з оцінкою тромбоцитозу, біохімічного сканування (альтітрансфераза (АЛТ), аспартатамінотрансфераза (АСТ), гамма-глутамілтранспептидаза (ГГТП), амилаза крові). Уровень інсуліну визначали за допомогою імунореактивного аналізу зі складом індексу інсулинорезистентності HOMA. Статистичний аналіз проведено з використанням програмного забезпечення Statistica 7.0 з допомогою дисперсійного аналізу (ANOVA) з наступним post hoc аналізом. Результати. У дітей 3-тій групи стеатозом поджелудочного жовчного міхура був виявлений низький рівень інсулинорезистентності, що дозволяє говорити про більш низький рівень стеатозу. Ключові слова: неалкогольна жирова болезнь печінки, неалкогольна жирова болезнь поджелудочного жовчного міхура, стеатометрія, еластографія.