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Pediatric non-alcoholic fatty liver disease: current thinking

Topic of the Month article

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Non-alcoholic fatty liver disease (NAFLD) is the most common pediatric liver disease in Europe, the exact prevalence is not well described, it ranges from 3 to 10% of general pediatric population. This percentage increases up to > 70%, with a male-to-female ratio of 2:1, in obese children. [1,2] Liver steatosis is recognized based on liver histology, but in clinical settings, surrogate markers (transaminases, ultrasound and other imaging techniques) are used for diagnosis. Still, the major problem is not to how to diagnose steatosis but predicting and recognizing the progression of liver disease to cirrhosis. The major therapeutic approach is based on weight reduction; however compliance is poor and other therapeutic options are sought. In this paper, we briefly described the recent publications with regard to diagnostic approaches, follow up and therapy.

Keywords:- fibrosis, NAFLD, NASH, steatosis

Diagnosis of NAFLD

Diagnosis may be made with liver biopsy, but reliable non-invasive tests are urgently required, as liver biopsy cannot be applied to all patients suspected of having NAFLD. We proposed a diagnostic approach to NAFLD in an ESPGHAN position paper[3]. The clinical diagnosis is usually made based on recognition of risk factors (central obesity), features of liver steatosis (ultrasound and increased transaminases) and exclusions of other diseases (including some metabolic diseases). Still, this approach is not ideal and does not allow for finding all NAFLD patients, or distinguish NASH from NAFLD. Liver biopsy is still required in selected patients, as described in ESPGHAN position paper. Recently, NASPGHAN position statement has been published which makes emphasis on ALT screening to early diagnose NAFLD among obese/overweight children. Still, the NASPGHAN statement is critical to ultrasound as a method to diagnose fatty liver. [4]

Non-invasive methods to assess liver steatosis and fibrosis are being developed and brought into practice.Controlled attenuation parameter (CAP) evaluated with transient elastography (FibroScan) has been recently applied for in non-invasive assessment of steatosis and was shown to be related to a significant steatosis in adult patients with NAFLD [5]. The method is simple and can be applied

easily in children,[6] but requires further pediatric studies and may give lower accuracy in extreme obesity. The latter can be largely overcome by using the special XL probe instead of the regular M probe;although this needs validation in children. Fibroscan combines evaluation of fibrosis and steatosis. Ultrasound still remains one of the methods used widely for diagnosis of fatty liver, however the limitations of this method should be taken into account, which is low in accuracy in mild steatosis and intraobserver variability.

More recently, Garcovich et al showed that shear-wave elastography (elastography used with regular ultrasound machine) is an accurate and reproducible non-invasive technique that efficiently depicts the presence of significant liver fibrosis and, less accurately, mild liver fibrosis in pediatric patients with nonalcoholic fatty liver disease. In his manuscript, elastography showed a very high correlation with liver fibrosis at univariate and multivariate analyses. The AUCs for the association of any and significant fibrosis were 0.92 (95% confidence interval [CI]: 0.86, 0.98) and 0.97 (95% CI: 0.95, 0.99), respectively.[7] MRI methods, such as proton density fat traction (PDFF) measurement and elastography (MRE), have been used to characterize pediatric liver disease, and are more accurate than ultrasound, but availability of hardware may be an issue. Multiparametric MRI (Liver*MultiScan*^{TM}), measuring liver iron, fat and fibroinflammatory disease, has been demonstrated in adults, and the liver inflammation-fibrosis score (LIF) has been shown to predict clinical outcomes. Applicability of this method for NAFLD has been reported recently in adults.[8] Pediatric validation is necessary. The major question is, however, not the extent of steatosis and fibrosis, but rather the risk of disease progression, which needs to be studied in longitudinal trials. In pediatric settings, there is limited data on liver histology to indicate prognostic features in NAFLD/NASH. Still, liver fibrosis is regarded to be a poor prognostic factor. Surrogate markers of fibrosis are urgently needed. Liver fibrosis in children can be detected by a combination of clinical and lab features, advanced biochemical markers or imaging techniques as recently summarized in a review paper. [9]. For clinical practice simple fibrosis scores have been developed to assess fibrosis in

children with NAFLD like the pediatric NAFLD fibrosis index (PNFI) elaborated in an Italian cohort by Nobili et al,[10] or pediatric NAFLD fibrosis score (PNFS), which has relatively high accuracy for advanced fibrosis, and incorporates simple determinants such as alkaline phosphatase, GGT, and platelets.[11] PNFI is a simple and non-invasive index based on age, waist circumference and triglycerides that could be used to predict liver fibrosis in children with NAFLD followed at tertiary care centers. The final model shows an area under the receiver operating characteristic curve (AUOC) of 0.85 for the prediction of fibrosis.[10] The PNFS is based on a multivariable logistic regression model including ALT, ALP, GGT and platelets count. The AUCROC for this model was 0.74 (95% CI: 0.66, 0.82), significantly better than other similar scores (APRI, NAFLD Fibrosis Score and FIB-4 Index). This score developed in a tertiary center care needs to be validated in other larger population in order to confirm its utility on large scale. [11]

Specific biochemical markers of hepatocyte cell death and extracellular matrix turnover like CK-18 [12] and hyaluronic acid [13] have been shown to correlate with the degree of fibrosis, but they may not be readily available, as compared to the previously described simple fibrosis scores. One may also question the use of elaborative diagnostic procedures, for NAFLD in children, if we have to treat obesity irrespective of its complications. There is growing data showing long-term consequences of early obesity and NAFLD in adulthood seems to be directly related to weight gain in childhood.[14] Perhaps we should change our primary goals, from making diagnosis of NAFLD, to defining the risk of developing cirrhosis in adulthood, in relationship to early obesity. The risk seems to be mediated by genetic factors which have been recently described, like the PNPLA3 rs738409 polymorphism associated already in youths with increased ALT. [15] In near future, we can expect testing for a combination of genetic risk factors and environmental factors, which will help in monitoring and making decisions on therapy. Still, at the moment, it seems to be reasonable to make early diagnoses of NAFLD, and to follow the patients, to pick up those with the high risk of disease progression.

Traditionally, NAFLD is regarded as part of metabolic syndrome and combined with cardiovascular disease. Increased blood pressure is claimed to be associated with NAFLD and doctors are advised to routinely measure blood pressure in their liver patients. [16] At present, we advise performing detailed diagnostic approach in all obese children, which should include assessment of lipid parametres, glucose tolerance, blood pressure, ultrasound of the liver and ALT/AST measurement. Our clinical practice indicates that fatty liver disease is commonly associated with insulin resistance and low HDL-cholesterol, however, other complications of obesity (hypertension, diabetes type II) are rarely seen in children with NAFLD, but it still needs to be looked for.

Comorbidities are also possible and in the ESPGHAN position statement it is advised to search for Wilson disease and alpha-1-antytrypsid deficiency in children suspected to have NAFLD.

Recently coeliac disease was found to coincide with NAFLD [17] and should be included into differential diagnosis. The common approach to make diagnosis of NAFLD is based on exclusions of other diseases presenting with liver steatosis. Diagnosis of NAFLD must be revisited once it responds poorly to weight reduction therapy.[3,4] We propose diagnostic approach to NAFLD which includes risk of fibrosis as presented on figure 1.

Treatment of pediatric NAFLD

The optimal goal of treatment of NAFLD, both in adults and children, is to halt and reverse the progression of liver damage and restore the normal architecture and function in the hepatic cells. Today, it is well established that weight loss is able to induce a significant improvement of both metabolic and hepatic features, mainly steatosis, in adult and pediatric obese subjects with NAFLD [18 19]. However, in children, several studies have reported that, despite all efforts, achieving and maintaining weight loss through behavioral intervention is very difficult, with < 10% success rate during 2 years intervention. For these reasons, the effective role of weight loss in the treatment of pediatric NAFLD is very limited and in the last years several studies have been made in order to

identify a useful pharmacological intervention to treat NAFLD. Therapeutic approaches are based on the mechanisms involved in NAFLD pathogenesis, including insulin resistance, oxidative stress and dyslipidemia.

Metformin is the main insulin-sensitizer evaluated in children; even if initial small studies seemed to demonstrate a positive laboratory and imaging effects of metformin in children affected by NAFLD [20 21 22 23], subsequent RCTs have not confirmed these results. Recently, a large randomized clinical trial (173 enrolled patients), called TONIC, confirmed that metformin was not effective in reducing serum transaminases levels and had no significant effect on liver histology. [24] Considering that metformin has no additional histological or biochemical effects ,other than its independent insulin-sensitizing role, it is not recommended as first line treatment for NAFLD.

Taking into account the central role of oxidative stress in the development of NAFLD damage, anti-oxidants have been evaluated as possible NAFLD treatment, primarily vitamin E. Similarly to metformin, although in the first small studies vitamin E, seemed to be useful in inducing an amelioration of serum transaminases levels, subsequent larger RCTs have not confirmed these results [19 25 26]. Also in the TONIC trial vitamin E was no better than placebo in attaining the primary end-points of reduction of transaminases serum levels, but a limited improvement in hepatocyte ballooning and in NAS score (Non-alcoholic fatty liver disease Activity Score) has been described. [24] In adults, better results were described for vitamin E and, therefore, larger studies with well-defined dosage of vitamin E are needed in children prior to considering it routinely, in the treatment of pediatric NAFLD.

An attractive field of interest in the last years in the treatment of pediatric NAFLD has been represented by nutritional supplementation, and omega-3-fatty acids and probiotics have been the main evaluated agents. Poly-unsaturated fatty acids (PUFA) are mainly constituted by omega-3 and omega-6, essential fatty acids which are competitively metabolized by the same pathways, with consequent anti- or pro-inflammatory effects. Some data have described an association between

altered omega-3/omega-6 ratio and NAFLD, metabolic syndrome and cardiovascular risk. In particular, in the last years, the Nonalcoholic Steatohepatitis Clinical Research Network reported a strict association between poor PUFA intake and hepatic inflammation in liver biopsy in children. [27] Recent studies showed the interesting mechanisms of action of docosahexaenoic acid (DHA) in the liver, which modulates the G protein-coupled receptor-120, exerting anti-inflammatory activity, and reduces the activation of hepatic progenitor cells, involved in the progression of liver damage[28], and in association to Vitamin D showed both an improvement in NAS score and a reduction of the activation of hepatic stellate cells and fibrillary collagen [29]. However, some of this studies where a mixture of DHA and EPA was used, it did not confirm this effect. [30] Although the available data on the use of omega-3 in children with NAFLD are still conflicting and drawn by small pediatrics trials, this approach continues to be more attractive, mainly for its safety and beneficial cardiovascular effects. Therefore, the possible therapeutic role of PUFA in treatment of NAFLD remains an open question, which can be further tested in larger clinical trials with other well defined end-points.

Following the discoveries of important roles played by gut in the pathogenesis of chronic liver diseases (the so-called "gut-liver axis"), and in particular in NAFLD pathogenesis, several animal and human studies have been made in order to better investigate this relationship and its possible therapeutic implications. The incorrect diet and the slowing intestinal transit, frequent in obese patients, seem to induce small intestinal bacterial overgrowth (SIBO), increasing the release of endotoxins, mainly of gut-derived lipopolysaccharides (LPS) and tumor necrosis factor (TNF) - alpha that cross the high permeable intestinal barrier of patients with NAFLD, promoting the progression of liver damage. Based on these data, probiotics, as manipulators of intestinal bacterial microbiota, have been tested in the treatment of FLD (28). Recently, Alisi and coworkers reported the first data on the use of VSL#3, a mixture of eight probiotic strains, in obese children affected by NAFLD, showing after 4 months of treatment a significant improvement in steatosis at ultrasound

examination and body mass index.[31] To date, only a few studies on probiotics in NAFLD are available. Therefore further larger and long-term studies are needed to define whether probiotics are a safe and effective long-term therapy for NAFLD in pediatric setting.

Actually, none of the tested drugs is totally satisfactory for the treatment of NAFLD; thus some clinical trials are ongoing, aiming to identify an optimal pharmacological treatment. Based on the recent advances in the knowledge of NAFLD pathogenesis, new molecular targets have been proposed, as suitable treatments and are now being evaluated; the newer trials use combination approaches which include different molecules directed towards specific pathogenic targets, or drugs that have shown sufficient evidence in adults with NAFLD. The results of the trial with DHA and vitamin D have been recently published in Plos One Journal.[29] Briefly in this manuscript, the Authors were able to show that DHA plus vitamin D treatment reduced the NAFLD Activity Score (NAS), in the treatment group (5.4 v1.92; $p<0.001$ for baseline versus end of study). There was no change in fibrosis score, but, different than the previous trial with DHA alone, a reduction of the activation of hepatic stellate cells (HSC) and fibrillar collagen content was noted (3.51±1.66 v. 1.59±1.37; $p = 0.003$) in treatment group. New randomized controlled trials are focused on the use of cysteamine, an amino-thiol with proved anti-oxidant and anti-inflammatory properties, and on angiotensin converting enzyme inhibitors, such as losartan, for their hypothesized anti-inflammatory and anti-fibrotic effects (NCT01913470). Moreover, bile acids seem to have also protective effect and recently obeticholic acid was tested in adults with promising results. The obeticholic acid is a potent activator of the farnesoid X nuclear receptor that reduces liver fat and fibrosis in animal models of FLD. In a recent multi-centre RCT conducted in the USA on adult patients with non-cirrhotic NASH, obeticholic acid improved the histological features of non-alcoholic steatohepatitis. Further larger studies are needed in order to confirm these interesting results and to verify its safety and tolerability on long-term. [32] An effective pharmacological therapy for NAFLD is still far away, however, some small steps forward have been made. An emerging and

interesting strategy in the treatment of selected cases of morbid obese children with non-alcoholic steatohepatitis (NASH) is bariatric surgery. Recent evidence suggested that bariatric surgical procedures may induce a significant improvement of liver histology, even in individuals with hepatic fibrosis. [33] [34] Encouraged by the good results observed in adults, bariatric surgery has been proposed in the treatment of morbidly complicated obesity in adolescents.[35] Recently, the Hepatology Committee of ESPGHAN proposed a society position statement about the indications for bariatric surgery in severely obese adolescents. In this paper, it has been suggested that bariatric surgery should be considered a therapeutic option in select morbidly obese adolescents with BMI > 40 kg/mq and severe comorbidities (including NASH with advanced fibrosis) or with BMI more than 50 kg/mq and mild comorbidities. [36] Applying these guidelines, recently the group by Nobili in Rome published their first 1-year trial after sleeve gastrectomy procedure in children affected by NAFLD and liver fibrosis. They found that Laparoscopic Sleeve Gastrectomy (LSG) was more effective than lifestyle intervention, even when combined with intragastric devices, for reducing NASH and liver fibrosis in obese adolescents after 1 year of treatment. [37] Moreover in this pilot study, the Authors did not observe any major perioperative complication in patients undergoing LSG or in those who received intragastric balloons, probably owing to the long experience of our surgeons. Obviously longitudinal and larger cohort studies are needed to compare the effectiveness of bariatric surgery with that of lifestyle intervention for preventing the progression of NAFLD early in its natural history, toward more severe forms of liver derangement.

In summary, there are new techniques improving diagnosis and treatment of NAFLD, but they require further validation in pediatric populations. The diagnosis is still based on risk factors (central obesity) and exclusions of other liver diseases, while ultrasound and liver tests can help in making diagnosis even if their accuracy is low. Weight reduction therapy should be the aim of treatment approach, however, the compliance is poor and pharmacological treatment would be helpful; DHA, some probiotics, vitamin E are to be considered, but the evidence is still not

sufficient. Those who do not respond to this therapy require closer investigations and careful follow up.

Follow up

To date, clear guidelines that define a protocol to follow up with patients with pediatric NAFLD are lacking. The main challenge for paediatric hepatologists is the identification of children with higher probability of progression to a more severe form of liver disease. Although several studies have aimed at identifying clinical parameters, or non-invasive markers, that can predict the progression of a liver disease, liver biopsy remains today the gold standard for diagnosis and monitoring liver damage. It is now widely accepted that children with NAFLD need to be regularly followed in order to supervise the progression of their liver and metabolic disease. The timing of follow up and the indication to repeat liver biopsy remain undefined and the decision depending on the clinical situation. Further larger longitudinal pediatric studies are needed in order to define the follow up protocol of pediatric NAFLD patients, also to provide informed counseling to patients and their families regarding their chronic disease.[38]

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Figure 1:Proposed management of an obese child with fatty liver