Pediatric NAFLD Diagnosis and Staging

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The increased prevalence of non-alcoholic fatty liver disease (NAFLD) requires special attention in pediatric patients, as it manifests in them in a more severe and progressive way compared to adults. The implementation of the appropriate therapeutic interventions is determinant of the attempts to treat it. For that purpose, early diagnosis and staging of the disease is essential.

Keywords: NAFLD ; pediatric NAFLD/NASH ; diagnosis ; ultrasound ; children

1. Introductory Elements

The rising prevalence of non-alcoholic fatty liver disease (NAFLD) and the possibility of its development into non-alcoholic steatohepatitis (NASH) and ultimately, to end-stage liver disease, makes its diagnosis a matter of great importance. Current management guidelines do not recommend screening tests for NAFLD in patients attending primary healthcare units or to high-risk patients (e.g., diabetic and obese patients). This is due to the unreliability of the diagnostic tools and to the lack of basic treatment options [1].

A meta-analysis reported that the risk for liver-induced mortality was 5.7 times higher for patients with NAFLD. Thus, it is suggested that the likelihood of NAFLD leading to morbidity and mortality depends on the severity of histological deterioration, especially in the presence of hepatic inflammation. Ref. [2] Children with pediatric NAFLD (pNAFLD) are at high risk of type 2 diabetes during early adulthood. Ref. [3] Recent data on the pediatric population have shown an alarming association among pNAFLD and cardiovascular risks, a finding that has not yet been confirmed for adults as well [4][5]. Progression of the disease could lead to the development of the severe fibrotic stage, which is referred to as pediatric non-alcoholic steatohepatitis (NASH) [6].

2. Serological Markers and Diagnosis

The advantages of serological indicator analyses are their wide applicability, the reproducibility of the results and their high availability. However, none of them are completely specific to the liver, and the results can be affected by coexisting pathological conditions; therefore, meticulous evaluation is required. Ref. [7] CK18 (Cytokeratin 18, released by hepatocytes during necrosis or apoptosis) and soluble Fas factor and its ligand (Fas Ligand) (markers of the external apoptosis pathway) are the main indicators [8][9]. Screening for ALT (alanine aminotransferase) levels should be performed with caution, as there are baseline discriminations among ALT levels between healthy-weighted adults and children, apart from several other risk factors that could potentially affect them as well [10].

An alternative approach could be the recording of biomarkers related to oxidative stress and inflammation, produced by different oxidative pathways. In a study of histologically confirmed NASH patients, lipid peroxidation was systematically measured in a control group with similar characteristics (BMI, sex, age), and both oxidized LDL and thiobarbitic acid reactives were found to increase in NAFLD patients. Ref. [11] In a similar study using mass spectroscopy techniques, it was shown that plasma products of the free oxidative radicals of linoleic acid were significantly increased in adult patients with NASH compared with patients with NAFLD and individuals with normal findings from liver biopsies [12].

3. Severity of Hepatic Fibrosis, Histological Findings and Diagnosis

The stage of hepatic fibrosis is the most crucial prognostic indicator for NAFLD and predicts the risk of developing cirrhosis and complications. [13] Indeed, two new milestone studies have identified hepatic fibrosis as the strongest predictor of long-term NAFLD outcomes, including liver-related mortality and overall patient mortality [14][15].

NAFLD-associated hepatic fibrosis presents in different stages, ranging from the absence of fibrosis (stage F0) to cirrhosis (stage F4), with stages of fibrosis F2–F4 being considered clinically significant and stages F3–F4 being

considered as advanced fibrosis. When interpreting non-invasive liver fibrosis tests, it is important to categorize the results based on a mild presence of fibrosis, a clinically significant fibrosis or an advanced fibrosis. Risk factors for the development of advanced fibrosis and cirrhosis are old age, severe obesity and the presence of metabolic syndrome [16]. Some routine clinical laboratory indicators have been created in recent years for the diagnosis and assessment of the severity of NAFLD. The most common is the AST (aspartate aminotransferase)/ALT (alanine aminotransferase) ratio (AST-to-ALT ratio (AAR [AST-to-ALT ratio])), while other indicators are the BARD score, the FIB4 index and the NAFLD fibrosis score (NFS) (in addition to the above, serum albumin values are included) [17].

Studies have shown that pediatric NAFLD exhibits features of NASH in almost half of the cases [18]. Pediatric NASH presents a unique histological pattern in comparison to adults [19]. There are two types of NASH proposed for describing the histologic evaluation: Type 1 is characterized by steatosis, ballooning degeneration and perisinusoidal fibrosis in both pediatric and adult patients, and Type 2, which is seen exclusively in pediatric patients, by the absence of ballooning degeneration and perisinusoidal fibrosis. Type 2 has mostly been observed in obese children of early age [18]. Those aforementioned characteristics make biopsy the “gold standard” for NASH in pediatric patients. However, biopsy in children should be avoided, and thus it is important to assess with non-invasive diagnostic alternatives [19]. Compared to adults, in terms of histological features, steatosis was found to be significantly more severe in pediatric NAFLD cases [18].

4. Classic Ultrasound

4.1. Data in Favor of the Use of Ultrasound in Pediatric NAFLD/NASH

Classic ultrasound (US) is the most widely used imaging method for the diagnosis of fatty liver filtration due to its high availability, its user-friendliness, its tolerance by the examinees and its low cost. Typical findings are based on the ultrasonographic comparison to the right renal parenchyma, the peripheral attenuation and the presence of areas with focal amplification of the ultrasound beam. Ref. [20] The degree of infiltration can be subjectively classified as mild, moderate or severe, or as suggested by some studies, can be classified using absolute ultrasound criteria. Ref. [21][22] During a meta-analysis (2815 patients with suspected or confirmed liver disease), the exact sensitivity and specificity of the ultrasound to distinguish moderate to severe fat infiltration from no filtration, as characterized after biopsy, was 85% (80–90%) and 93% (87–97%), respectively. This study involved adult patients [23]. In children, liver US for fat detection presented a sensitivity of 70% to 85% and specificity of 50% to 60% [10][24]. Despite the diagnostic limitations for people with co-occurring kidney disease and obese patients found in the aforementioned study [23], the European directives for the management of NAFLD recommend the use of ultrasound as the first-choice imaging for people with suspected NAFLD/NASH [25].

A large pediatric cohort study showed a positive correlation between ultrasound degree of fatty infiltration and histologically established severity of the disease [26]. In the same study, a particularly interesting finding was the lack of a positive correlation between transaminase values with either ultrasound or histological findings, suggesting a lower diagnostic value of these markers in pediatric patients. Ultrasound was considered an effective tool for the staging and screening of these patients [26]. Interestingly, there has been a higher incidence of NAFLD/NASH in obese children with steatosis upon biopsy, which makes it a possible risk factor for the disease. Therefore, it is important to note that the combination of fatty liver on ultrasound with a high serum ALT value increased the detection of NAFLD in children in these highly suspected groups [27]. However, there was a remarkable percentage with conspicuous fatty infiltration on ultrasound and unaffected value of ALT in serum. In addition, it was found that children with fatty infiltration and a normal ALT value did not usually show other manifestations of metabolic syndrome. These studies rendered the ultrasound an effective tool for screening NAFLD/NASH in the suspected pediatric population, in contrast to the measurement of serum aminotransferases, which in the current literature seem to be insufficient [28]. A study in Egypt showed 100% sensitivity and 10% specificity in the detection of histologically confirmed NAFLD via ultrasound examination. Therefore, it was concluded that the absence of ultrasound or the presence of grade “A” hepatic infiltration could safely rule out histology and prevent biopsy [29].

To support the above, the use of ultrasound as a screening tool for pNAFLD/NASH showed high sensitivity but low specificity for fat infiltration in highly obese children [30]. To aid the diagnosis, MRE (magnetic resonance elastography) was proposed to detect the presence or absence of fibrosis. In an attempt to quantify the fatty infiltration by ultrasound (>5% of infiltration), there was a significant overlap with the findings of the MRE (classification: absence, mild, moderate and severe infiltration) [30]. In another group of children with histologically confirmed NAFLD, the ultrasound findings of fatty infiltration appeared to correlate well with the corresponding clinical parameters and liver pathology. In addition, the degree of hepatic fat infiltration was correlated with the fibrosis stage, and it was associated with higher BMI (body mass index), waist circumference, hematocrit and insulin resistance [31][32]. Regarding NASH, ultrasonography can provide a

valid outcome, provided the use of US contrast matter, as a significant decrease has been found on the uptake of the contrast in NASH patients [33]. In addition to that, a new US fatty liver indicator score, based on the intensity of liver contrast, has been found to successfully evaluate the pathologic criteria for NASH, proving the usefulness of US for staging the disease in pediatric patients [21].

4.2. Non-Encouraging–Conflicting Findings

There are some practical limitations that undoubtedly reduce the diagnostic sensitivity of ultrasound in obese children, who are usually candidates for developing pNAFLD. The diagnostic sensitivity of the method is reduced either when the liver parenchyma contains percentages of fat below 30% or in people with a body mass index of 40 or more. In addition, ultrasound cannot detect the presence of steatohepatitis or fibrosis. In general, for the adult population, the sensitivity of ultrasound for the diagnosis of NASH varies from 60% to 90% with a specificity of 84% to 100%. The differences among NASH and NAFLD are not conspicuous via radiological diagnostic tools [34]. The limitations of traditional US diagnosis for pediatric patients could be eliminated by novel technologies such as controlled attenuation parameters that could detect steatosis [10].

Some opponents of the use of US argue that the low sensitivity and specificity of the method for the diagnosis and determination of fatty infiltration makes it unsuitable and inaccurate for the application of population screening for NAFLD/NASH in children. Despite the universally accepted fact that ultrasound is widely available and can rule out the presence of liver masses, cysts or bile pathology, a normal liver ultrasound cannot rule out the existence of NAFLD with absolute certainty and therefore, it is not preferred [35]. Ultrasound was also used to diagnose NAFLD with a positive prognostic value of 47% and 62%. No stable correlation was found between ultrasonic fatty infiltration and reference measurements. That does not clearly lead to the exclusion of ultrasound as a screening medium for NAFLD, but it rejects it for the staging of fat infiltration in children [36]. The same applies to the diagnosis of NASH. Several studies observed the limitations of US in NASH diagnosis, especially for obese patients and patients with hepatosteatosis less than 30% [37].

Thankfully, new technological extensions of the classic ultrasound have emerged to satisfactorily cover the need for staging of NAFLD/NASH not only in children, but also in the adult population.

4.3. Ultrasound and Evaluation of Therapeutic Interventions

Ultrasound seems to be used quite effectively in its classic form for the evaluation of interventions in children with NAFLD after specific periods in which a change in the metabolic profile is anticipated. A 12-month program that included diet and physical activity resulted in a significant reduction in BMI and fasting glucose, insulin, lipid and liver enzyme levels as well as hepatic ultrasound findings on conventional ultrasound [10]. Any degree of reduction in excess weight was associated with a significant reduction in the impact of NAFLD. Even a minimal reduction in excess weight led to a significant improvement in the ultrasound image, due to the reduction of fatty filtration [38].

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