Characterization of NASH
Histology

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The only chronic liver disease whose definition is based solely on histology
Characterization of NASH: Histology

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. Draft Guidance from Food and Drug Administration, December 2018

« Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of histological changes that begin with simple fatty infiltration of the liver (NAFL), which may gradually progress to the development of chronic inflammation (steatohepatitis or NASH), fibrosis, and ultimately cirrhosis. .............. Currently, there are no clear criteria to identify this group of patients.”

→ If a diagnosis of NASH is required, then liver biopsy is mandatory
Liver biopsy is a reliable procedure
Liver biopsy is a reliable procedure

- **Sampling issue**: A 20mm biopsy done with a 16 Gauge needle provides enough material for robust diagnosis of NASH.

- **Observer variation**: not an issue between experienced liver pathologists using clearly-defined histological criteria.
Liver biopsy: a reliable procedure

- **Sampling issue:** A 20mm biopsy done with a 16 Gauge needle provides enough material for robust diagnosis of NASH

- **Observer variation:** not an issue between experienced liver pathologists using clearly-defined histological criteria *(NASH CRN 2005, FLIP, 2014)*

→ Training and experience are essential for:
  - the hepatologist/radiologist who will perform the biopsy
  - the pathology lab that will prepare the sections
  - the liver pathologist who will review the section
Histological characterization of NASH

- Acute Alcoholic Hepatitis-like: Steatosis + Mallory hyaline + Polymorphonuclear
  

- Steatosis + ballooning + mixed acute and chronic lobular inflammation + zone 3 perisinusoidal fibrosis
  
  *(Brunt E. Am J Gastroenterol 1999;94:2467–2474)*

- Steatosis + inflammation + hepatocellular ballooning
  

  - NAS ≥ 4 and 1 point in each category (clinical trials)
  
  *(Draft Guidance from Food and Drug Administration, December 2018)*

→ A shift from a rare and severe disease to a wide histological spectrum including mainly minor histological diseases
NAFLD Activity Score (NAS, 0-8)

STEATOSIS

1

2

3

+ BALLONING

1

2

+ INFLAMMATION

1

2

3

NASH CRN, Hepatology 2005
NASH - NAS = 5

→ 1 + 2 + 2

3 + 1 + 1 →
Shifting from a dichotomized to an analytical classification

NAFLD

STEATOSIS (NAFL)

STEATOHEPATITIS (NASH)

STEATOSIS IS THE MARKER

ACTIVITY THE DRIVER

FIBROSIS THE KILLER
Stage of Fibrosis (Kleiner et al, Hepatology 2005)
LIVER FIBROSIS: MAJOR PROGNOSTIC FACTOR

Liver-related mortality according to stage of fibrosis in index biopsy

Overall survival according to fibrosis stage and compared to control population


Liver biopsy interpretation
Integrative classification (FLIP consortium, SAF)

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Liver biopsy interpretation
Integrative classification (FLIP consortium, SAF)

STEATOSIS
THE MARKER

ACTIVITY
THE DRIVER

FIBROSIS
THE KILLER

Take-home messages

• NASH is defined by histology. If a diagnosis is needed (clinical trials…) then liver biopsy is mandatory.

• Liver biopsy is a robust procedure that can assess all components of NAFLD if performed by trained physicians (hepatologists and pathologists).

• An analytical description that reports Activity and Fibrosis in a semi-linear fashion is more appropriate than a dichotomous classification (NASH vs No NASH).

• LB is obviously not a screening tool and biomarkers are strongly needed to select patients at high risk of severe disease and who will need a biopsy.

• BUT…
THE WHOLE LIVER
The perfect standard
Sharp image

LIVER BIOPSY
Estimator of the perfect standard
Fuzzy picture

NON INVASIVE BIOMARKER
Estimator of the Estimator
Misty picture
Predicting histology with a biomarker
THANK YOU FOR YOUR ATTENTION!

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