MINI REVIEW

Focal nodular hyperplasia, hepatocellular adenomas: Past, present, future

Hyperplasie nodulaire focale, adénomes hépatocellulaires : passé, présent, futur

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Past

In the 1958 monograph on liver tumors, Edmondson established that we have to distinguish between two basically different forms of benign liver tumors. For one, he reserved the designation hepatocellular adenoma (HCA), for the second the term focal nodular hyperplasia (FNH) [1].

Present

HCA

The estimate prevalence is 3—4/100,000 in Europe and North America. Genomic and molecular studies [2,3], together with the analysis of the genotype/phenotype correlations [4,5], have led to the recognition of three major HCA subgroups: HNF1α inactivated, inflammatory and β-catenin activated HCA. Sixty per cent of the inflammatory HCA are also gp130 mutated [6]. While immunohistochemistry (Fig. 1) identifies the three major subgroups, MRI identifies HNF1α inactivated HCA and inflammatory HCA [5,7]. Unusual clinical manifestations such as inflammatory anemia or nephrotic syndrome can be observed in inflammatory HCA [8]. Familial cases of adenomatosis can also be found in HNF1α inactivated HCA [9,10].

FNH

The estimate prevalence is 10 times greater than HCA. Most of the FNH are polyclonal tumors [11,12]. Molecular analyses has identified ANGPT1/ANGPT2 and NTS/HAL ratio of gene expression that are highly increased in FNH compared with normal liver, hepatocellular carcinoma or adenoma [12,13]. The β-catenin pathway is activated heterogeneously in FNH without β-catenin or Axin1 mutation [14]. Glutamine synthase has been proposed as a marker to identify FNH [15]. Contrast ultrasound and MRI allows the identification of FNH in the great majority of cases.

What remains true of the past

What remains true of the past are:

• the great majority of HCA occurs in women taking oral contraceptives [16]. Once discovered, oral contraception should be stopped;

Figure 1 Phenotypic classification of HCA in patients without known etiology except OC (Bordeaux experience based on 130 cases). The dotted line separates the different subgroups in women. The different subgroups in men are in between the thick lines.

- all possible causes should be considered (Table 1);
- the main risk factor is bleeding (incidence 25%). Malignant transformation of HCA is rare (5–7%). Size (> 5 cm) is an important determinant for these two risks [17,18].

**What remains true but needs to be updated**

What remains true but needs to be updated are:

- familial diabetes [19]. In rare families with an inherited mutation in one allele of HNF1A, MODY3 (Maturity Onset Diabetes of the Young type 3) patients are predisposed to develop familial liver adenomatosis with HNF1α inactivated HCA [9,10]. Obesity is also a risk factor for inflammatory HCA development [5,20]. Thus, relationship between metabolism perturbations and adenoma occurrence remains to be explored in detailed [21];
- HCA and hepatocellular carcinoma [22]. Malignant transformation occurs mainly in the β-catenin mutated group [4,17]. However, other HCA subtypes can also transform and these rare at risk lesions have to be identified.

**What needs revision**

What needs revision are:

- adenomatosis [23]. It is no longer a specific entity [17,18]. If used the term should mean many HCA (more than 10 and preferably unnumbered);
- telangiectatic FNH described as a subtype of FNH [24] are, at least for many of them, inflammatory HCA [20,25] (Fig. 1). To avoid confusion this term should be banned.

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HPS: hepatoporal sclerosis; FAP: familial adenomatosis polyposis.

a There is very little information in the literature (in our institution, nine patients are included in this series).
b Case report.
c Case report: focal nodular hyperplasia are more often reported.
Focal nodular hyperplasia, hepatocellular adenomas

- absence of ductules, a classical hallmark in HCA definition [27]. Ductules can be seen in inflammatory HCA [21].

Future

HCA

Basic science

The search for new gene mutations needs to go on and the present known mutations looked for on a large scale in different countries, particularly those where the use of oral contraception is not widespread. To understand the molecular steps in carcinogenesis particularly via the β-catenin pathway but also how HNF1α inactivation promotes lipogenesis and activation of several carcinogenic pathways [28,29]. To define the role of cofactors such as obesity present in 50% of inflammatory HCA and steatohepatitis.

Clinical science

To find the relevance of the genotype/phenotype classification in the management/follow-up and treatment [30]. To define the role of the biopsy and the place of new radical treatment avoiding surgery (radio frequency, embolization). Ultimately to test drugs that may block pathways involved in the tumoral process.

FNH

To identify (imaging, pathology) FNH lacking full blown criteria, and understand the genesis of their formation (normal and pathologic livers particularly cirrhotic ones), and the relationship between FNH (often multiple) and associated disorders such as brain tumors [25].

FNH, for the first time, will now have an International Classification of Disease (ICD) code, as it was decided for the next WHO revision book [31].

Conclusion

The differential diagnosis between FNH and HCA and between HCA and hepatocellular carcinoma is occasionally difficult and this difficulty increases when tumors are developed on pathological livers. The genotypic/phenotypic classification and we hope its further refinement, will remain the best way to avoid erroneous or doubtful diagnosis, and to adapt treatment according to each subtype.

References

in hepatocellular adenoma differs from that in MODY3 patients and suggests genotoxic damage. Diabetes 2010, 14 (online).


