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: HNF1\textsubscript{\alpha} inactivated, inflammatory and \beta-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 identifiers HNF1\textsubscript{\alpha} inactivated HCA and inflammatory HCA [5,7]. Unusual clinical manifestations such as inflammatory anaemia or nephrotic syndrome can be observed in inflammatory HCA [8]. Familial cases of adenomatosis can also be found in HNF1\textsubscript{\alpha} 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 \beta-catenin pathway is activated heterogeneously in FNH without \beta-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 focal 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

Table 1  Hepatocellular adenosomas: rare causes.

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>Causes</th>
<th>Genotypic/phenotypic classification</th>
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<tbody>
<tr>
<td>Women (young)</td>
<td>Polycystic ovary syndrome^b</td>
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<tr>
<td>Women/Men/Children</td>
<td>Metabolic</td>
<td></td>
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<td></td>
<td>Glycogenosis (I and III)</td>
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<tr>
<td></td>
<td>Galactosemia^b</td>
<td></td>
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<tr>
<td></td>
<td>Tyrosinemia^b</td>
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<tr>
<td>Genetic</td>
<td>MODY 3 diabetes</td>
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<td></td>
<td>FAP^b</td>
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<td></td>
<td>Peutz–Jeghers Syndrome^b</td>
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<tr>
<td>Drugs</td>
<td>Anabolic androgenic steroids</td>
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<td></td>
<td>i.e. Danazol</td>
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<tr>
<td></td>
<td>Antiepileptic</td>
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<tr>
<td></td>
<td>Carmabazepine^b</td>
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<td></td>
<td>Valproate^b</td>
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<td></td>
<td>Iron overload</td>
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<td></td>
<td>i.e. Fanconi anemia^b</td>
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<tr>
<td>Vascular disorders</td>
<td>Portal vein (agenesis, shunts, HPS)</td>
<td>IHCA</td>
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<td></td>
<td>Hepatic vein (Budd Chiari)</td>
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</table>

HPS: hepatoportal 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

References


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


