Focal Nodular hyperplasia

Eliezer Zahra Bianco[1], Martina Sciberras[1], Kelvin Cortis[2], Pierre Ellul[1]

Abstract

Hepatic Focal Nodular Hyperplasia (FNH) is a benign lesion characterized by the proliferation of hepatocytes and non-parenchymal cells. The etiology remains unclear. However, the higher female preponderance and the fact that FNH may grow in size during pregnancy may suggest a hormonal influence. These tumors are typically discovered incidentally on ultrasonography, computed tomography or magnetic resonance imaging. These imaging modalities reveal the characteristic "spoke-wheel" pattern of arterial enhancement, which is highly suggestive of FNH. Confirmation via histological examination may be necessary in cases of diagnostic uncertainty. In most instances, FNH is a benign and self-limited condition that does not necessitate treatment. However, surgical resection may be considered if the lesion is symptomatic or enlarging. Liver-sparing surgical techniques are preferred to preserve hepatic function. In conclusion, FNH is a benign hepatic lesion predominantly affecting women of childbearing age. Its characteristic radiological features and generally indolent course make it distinguishable from malignant liver lesions. Clinicians should consider conservative management and close monitoring in most cases, reserving surgical intervention for specific indications.

Key words: *Focal Nodular Hyperplasia; imaging; liver*

INTRODUCTION

Asymptomatic benign liver lesions are being increasingly identified on abdominal imaging. First described in 1958 by pathologist Hugh Edmonson M.D., focal nodular hyperplasia (FNH) is the second most common of such solid benign lesions, only surpassed by hemangiomas. Table 1 demonstrates the most commonly encountered benign liver lesions [1].

OBJECTIVES

The aims of this short literature review were to assess the epidemiology and etiology of FNH, explore the clinical presentation and diagnostic challenges including differential diagnoses, and characterize radiological and histopathological features of said lesions. Efforts were also made to evaluate its management and surveillance strategies.

METHODOLOGY

This literature review was conducted through two databases: PubMed and Google Scholar. The primary keywords used included "Focal Nodular Hyperplasia", "FNH", "Hemangioma" and "Benign Liver tumors". Boolean operators ("AND", "OR") were used. Only articles published in English and involving humans were used. Articles pertaining to epidemiology, etiology, clinical presentation, radio-histopathological features, and management were retrieved. Only articles published from the year 2000 onwards were included in this literature review.

EPIDEMIOLOGY

FNH is found in 0.3-3% of the adult population, most commonly in the 30-40 age group [1]. In contrast, it is found in 0.02% of the pediatric population [2]. Developing factors might shed light as to why there is a dif-

[1]Department of Gastroenterology, Mater Dei Hospital, Msida, Malta
[2]Department of Radiology, Mater Dei Hospital, Msida, Malta
Received: 08 Oct 2023; Accepted: 11 Dec 2023

Table 1. *Solid Benign liver lesions [1].*

Liver Lesion	Incidence in the adult population (%)
Hemangiomas	3-20%
Focal nodular hyperplasia	0.3-3%
Hepatic Lipoma	1%
Hepatocellular adenomas	0.007-0.0012%
Biliary Duct Hamartoma	0.6 – 5.6%
Nodular regenerative hyperplasia	0.72%-2.6%

ference in FNH incidence between adults and children. A pediatric liver is still developing and hence might be less susceptible to hormonal or vascular changes which are key in the pathogenesis of FNH. These lesions tend to be asymptomatic, and children usually undergo less transabdominal imaging than adults, thus leading to underdiagnosis [3].

In both adults and pediatric patients, there is a female preponderance, with a female to male ratio of 9:1 being reached in adults [1].

Although FNH is most commonly found as one lesion, around 20-30% of cases involve multiple lesions (usually up to 5). The latter can occur in patients with vascular liver disorders such as hereditary hemorrhagic telangiectasia and Budd Chiari syndrome [4]. It is very rare for FNH to present with more than 5 separate lesions in the same individual [5]. In the pediatric setting, it has been reported in long term malignancy survivors raising the suspicion that bone marrow transplant and chemotherapeutic agents (including high dose alkylating agents) increase the risk of FNH development in this population [6].

The size of FNH can vary. The vast majority are less than 5 cm and near the liver surface. Cases of FNH larger than 10cm have been reported and these are usually resected [7].

ETIOLOGY

The exact etiology and pathogenesis of FNH are not yet fully understood. A characteristic feature of FNH when compared to other benign liver lesions is its origin. It arises from polyclonal cells resulting in a number of modifications including angiopoietin vascular remodeling [8,9].

FNH is therefore thought to occur following a hyperplastic reaction in the liver in response to a vascular malformation. Change in the oxygenation of liver parenchyma is the initial focus of FNH. Continued ischemia leads to the proliferation of bile ducts [10]. Both increase and decrease in blood flow have been found to have the potential to cause a hyperplastic reaction in the liver [8]. In fact, an increased incidence of FNH in conditions with vascular malformations has been reported such as in patients with hereditary hemorrhagic telangiectasia and hemangiomas [11,12]. Up to 20% of FNH lesions can be associated with hemangiomas [9].

While the exact etiology remains elusive, several studies have identified certain molecular patterns for FNH. Of these, increased expression of extracellular matrix genes leading to activation of transforming growth factor beta (TGF-b) is prominent [13]. Increased production of glutamine synthase through overexpression of the Wnt/ B-catenin target gene is also observed [14]. The latter leads to map-like pattern expression of glutamine synthase at the edges of the lesion, a feature unique to FNH [14].

FNH has also been described in response to blunt abdominal trauma and exposure to certain chemotherapeutic agents, particularly alkylating agents, and drugs such as azathioprine [15]. Smoking seems to increase the risk of FNH. A diet high in vegetables and whole grains may decrease the risk of FNH [16]. In animal models, a high-cholesterol diet has been associated with an increased risk of FNH. The relationship between these diets and FNH could be explained by an increase in TGF-B1 protein expression [17].

RELATIONSHIP WITH PREGNANCY AND ORAL CONTRACEPTIVE USE

There is a controversy about the relationship between FNH and hormones. The increased incidence in females suggests a correlation with estrogen. Moreover, females on oral contraceptives tend to have larger nodules than their male counterparts and females not on oral contraceptive medications [8].

Several cases have been described showing a reduction in FNH size following the withdrawal of the oral contraceptive pill (OCP). Other cases highlight size progression in pregnancy and regression following delivery [4]. Nevertheless, the European Association for the Study of the Liver (EASL) guidelines states that studies have not yet established the role of pregnancy and OCP in the development of FNH [9]. Furthermore, FNH runs a benign course in pregnancy [4] (Figure 1). Vaginal delivery is not associated with an increased risk

of complications [18]. The American College of Gastroenterology (ACG) guidelines make similar statements and advise that pregnancy and the use of OCP are not contraindicated in patients with FNH [19]. Female patients who have FNH and wish to continue OCP should be monitored every 2-3 years [19].

HISTOPATHOLOGY

Microscopically, one of the distinctive features is a central scar which is made up of collagen, arteries, and veins. Fibrous septae might be present which will form a pseudocapsule. These characteristics allow the histopathologist to differentiate FNH from other similar lesions including hepatocellular carcinoma, hepatocellular adenoma (HCA), and fibrolamellar hepatocellular carcinoma. FNH might also contain Kupfer cells and bile ducts [8].

Other histopathological characteristics have been described. The most prevalent of these include the absence of the classical central scar. This usually occurs in lesions that are less than 3cm in size. Another atypical finding is FNH with steatosis. Immunohistochemistry staining is commonly used in the assessment of FNH. Glutamine synthase expression in a map-like pattern at the peripheries of the nodule is unique to FNH [9]. The latter can be used in instances when imaging is unable to differentiate FNH from HCA [19].

DIAGNOSIS

Diagnosis is usually based on imaging. Histological diagnosis can be obtained in doubtful cases. Although ultrasound (US) may be the first imaging modality used to assess liver nodules, magnetic resonance imaging (MRI) is considered the best modality when it comes to diagnosing FNH. It has a specificity of almost 100% and a sensitivity of around 75%. The latter decreases in small FNH (<3cm). In this case, especially if the lesion is <3cm in size, a combination of contrast-enhanced ultrasound (CEUS) and MRI is usually performed [4]. The addition of hepatobiliary contrast media – such as gadobenate dimeglumine- can increase the sensitivity of MRI to 99% [8].

RADIOLOGICAL FEATURES

Focal nodular hyperplastic lesions have typical findings on US, computed tomography, and magnetic resonance imaging. This lesion is considered to be homogenous in most imaging modalities, except for the central scar. US assessment usually depicts a hypo or isoechoic lesion. CEUS depicts the characteristic "spoke on wheel" sign on the arterial phase in which centrifugal arteries radiate from a central artery [20]. CT scans show a homogeneous hyperdense lesion in the arterial phase which becomes hypo or isodense in the portal phase. T1-weighted images on MRI depict the lesion as iso or hypointense. Central scar is enhanced in the delayed phase using gadolinium. T2-weight images produce a hyper or isointense lesion [19]. FNH shows mild diffusion restriction on diffusion-weighted MRI. The central scar is best appreciated on MRI [4]. Table 2 summarizes the FNH radiological characteristics of the different radiological tests.

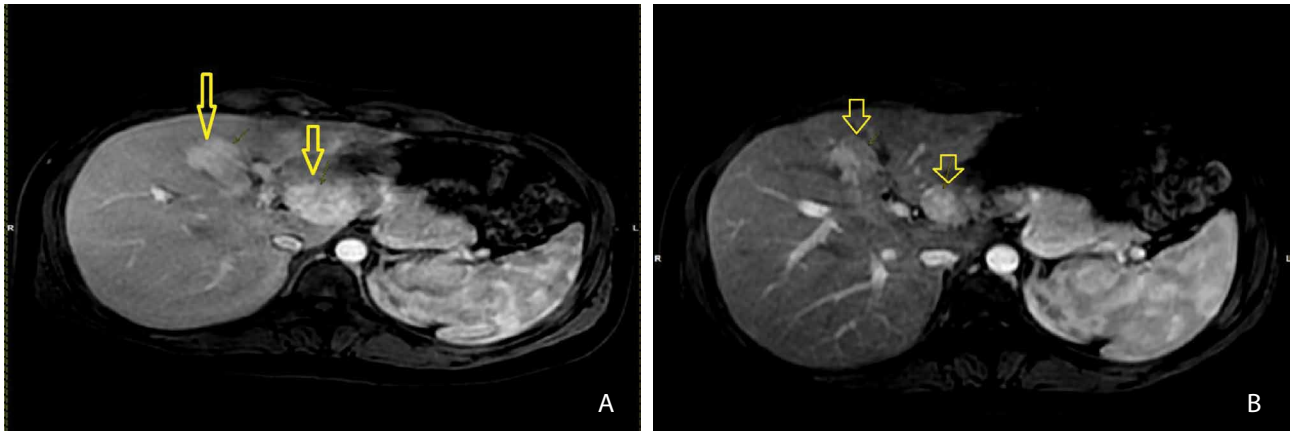

Figure 1. A and B: MR Liver/ Spleen arterial phase of a 28-year-old lady attending visits a Mater Dei Hospital, Malta. The patient was pregnant during the first MR Liver / Spleen (Figure 1A). The MR Liver/ Spleen was repeated in the following year (Figure 1B). Yellow arrows depict the presence of FNH in segments I and IV. One can easily appreciate the decrease in size of FNH from April 2021 (1A) to June 2022 (1B). Pregnancy was uneventful and no FNH-related complications occurred.

Table 2. *Radiological characteristics of FNH [7,19,28,29].*

Modality	Radiological Features
US	• Variable echogenicitiy • Doppler depicts increased vascularity in a centrifugal manner from a central vessel
CE-US	• Early arterial phase – Early enhancement with early centrifugal filling • Late arterial phase – Centrifugal filling • Portal venous phase – Enhancement – Scar may be visible (unenhanced)
CT	• Non-contrast – Hypo or isoattenuation – May appear hyperattenuating in cases of NASH • Arterial phase – Enhancement except central scar • Portal venous phase – Hyper or isoattenuation in contrast to the surrounding liver – Central scar retains hypoattenuation
MRI	• T1 – Iso or hypointense – Central scar is hypointense • T2 – Iso or hyperintense – Central scar is hyperintense • Gadolinium – Arterial phase: early enhancement – Portal venous phase: iso-hyperintense – Central scar retains contrast in delayed phases • Primovist – Arterial phase: early enhancement – Delayed arterial phase: enhances – Hepatobiliary phase: iso-tense, centra scar does not enhance
Tc-99m	• Sulfur colloid – Normal or increase uptake • HIDA – Increased uptake and delayed clearance

US: ultrasound; CE-US: Contrast enhanced ultrasonography; CT: Computed tomography; MR: Magnetic Resonance Imaging; Tc-99m: Technetium-99m; HIDA: hepatobiliary iminodiacetic acid

RADIOLOGICAL FNH MIMICKERS

Differential diagnosis of FNH includes other benign liver lesions as well as malignant ones. A feature similar to the "central scar" can be seen in fibrolamellar hepatocellular carcinoma, intrahepatic cholangiocarcinoma and HCA. It is important to differentiate FNH from the latter as HCA`s are associated with hemorrhage and malignant transformation [10]. US assessment of HCA depicts a heterogenous lesion which can be anechoic if bleeding or hyperechoic if steatotic. Cross-sectional imaging usually demonstrates a well demarcated lesion with peripheral enhancement [19].

Hemangiomas on the other hand are seen as hyperechoic nodules on ultrasonography and appear to have discontinuous peripheral enhancement with centripetal fill-in on cross-sectional imaging.

CLINICAL COURSE AND COMPLICATIONS

FNH is usually diagnosed incidentally through imaging, and most are therefore asymptomatic. Non-specific abdominal symptoms including early satiety and dyspepsia have been described. Abdominal pain may occur in large lesions due to compression of the liver capsule or pressure on surrounding organs [10]. An abdominal mass might be palpated in very large lesions. Biochemistry usually shows normal or mild derangement in liver enzymes, albeit this might be attributed to other underlying conditions. Of note, alpha-fetoprotein levels are normal [8].

The clinical course of FNH is usually benign. Malignancy has never been reported [21]. However, FNH has been reported to occur in association with other malignancies including hepatocellular carcinomas [22]. In FNH located near the liver surface, a rare complication that can occur is spontaneous intraperitoneal hemorrhage and rupture. This has been described in 10 cases so far (Table 3) [23]. The vast majority were women [23]. Fatal rupture and hemorrhage occurred in one patient in late pregnancy [24]. The preferred treatment option in this setting has been surgery [22,25].

MANAGEMENT

Both the European and American guidelines suggest a conservative approach to the management of FNH [9,19]. There is a poor correlation between FNH and symptoms; thus, conservative management is preferred even in the presence of non-specific symptoms. Active management in the form of surgical resection is only performed in specific cases such as in enlarging (usually a diameter of >7cm) and exophytic lesions. Another indication for resection is symptomatic FNH (as discussed above). The most common surgical option is usually hepatic resection. Both open and laparoscopic resection

Table 3. *Cases involving rupture of FNH [23].*

Patient Number	Year of publication	Age	Sex	Number of lesions	Maximal diameter (CM)	Management
1	1974	26	F	1	10	Surgery
2	1995	28	F	2	4.5	Surgery
3	2001	37	F	1	5	Pre-op TAE, Surgery
4	2003	27	F	1	6	Surgery
5	2005	35	F	1	9.8	Surgery
6	2005	42	F	1	10	Surgery
7	2006	37	F	4	5.2	Surgery
8	2006	26	F	N/M	15	Pre-op TAE, Surgery
9	2013	23	F	1	1	Diagnosis at Autopsy
10	2016	35	M	1	8	Pre-op TAE, Surgery

F: Female; M: Male; N/M: Not mentioned; CM: Centimetres; TAE: Trans-aterial chemoembolization

have been described [26]. Locoregional therapy in the form of embolization and radiofrequency ablation has been used in some patients, especially in those not fit for more invasive surgery [5,19].

SURVEILLANCE

Surveillance is generally not recommended. However, there is a difference in the recommendations of European and American guidance. According to European guidelines, once a diagnosis of FNH is made, there is no need for follow-up even in pregnancy and in patients on OCP. Furthermore, stopping oral contraceptive medications is not recommended [4]. Nonetheless, the American guidelines suggest annual ultrasonography assessment for 2-3 years after diagnosis is made in women who would like to continue oral contraceptive medication. Patients diagnosed with FNH and who are not on OCP do not require regular follow-up [19].

In patients diagnosed with FNH and who become pregnant, European guidelines do not recommend imaging surveillance [18]. At present, there is no guidance on females who are on hormone replacement therapy (HRT) and have concomitant FNH. It has been noted that hepatic hemangiomas which are commonly associated with FNH do increase in size and can rupture in women on oestrogen-based HRT [27].

CONCLUSION

FNH is a benign liver lesion frequently discovered incidentally. Its diagnosis can precipitate patient anxiety. Accurate diagnosis and appropriate management are crucial to avoid unnecessary interventions. Further research is warranted to enhance our understanding of FNH and improve its diagnosis and management.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

Author contributions: *EZB, the corresponding author was responsible for the literature review and drafting of the manuscript; MS helped with the literature review; KC provided and annotated figures 1A and 1B; PE participated in the design of this literature review and supervised this manuscript.*

REFERENCES

1. Oldhafer KJ, Habbel V, Horling K, Makridis G, Wagner KC. Benign Liver Tumors. Visc Med. 2020;36(4):292-303.
2. Lucas B, Ravishankar S, Pateva I. Pediatric Primary Hepatic Tumors: Diagnostic Considerations. Diagnostics (Basel). 2021;11(2):333.
3. Islam N, Halder A, Ghosh R, Banerjee S, Mishra P, Chatterjee U. Focal nodular hyperplasia of the liver in children: A report of 2 cases. Indian J Pathol Microbiol. 2019;62(2):261-5.
4. Ashhab AA, Abu-Sulb A, Yang JD, Noureddin M, Sundaram V, Kuo A, et al. Estrogen-Driven Growth of Focal Nodular Hyperplasia: Truth or Myth? ACG Case Rep J. 2021;8(1):e00531.
5. Kayhan A, Venu N, Lakadamyalı H, Jensen D, Oto A. Multiple progressive focal nodular hyperplasia lesions of liver in a patient with hemosiderosis. World J Radiol. 2010;2(10):405-9.
6. Franchi-Abella S, Branchereau S. Benign Hepatocellular Tumors in Children: Focal Nodular Hyperplasia and Hepatocellular Adenoma. Int J Hepatol. 2013;2013:215064.

7. Gaillard F, Šedivý O, Knipe H, et al. Focal nodular hyperplasia. 2023; Available at: https://radiopaedia.org/articles/6749. Accessed 03 Sep, 2023.
8. Hamad S, Willyard CE, Mukherjee S. Focal Nodular Hyperplasia. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532244/
9. European Association for the Study of the Liver, (EASL). EASL Clinical Practice Guidelines on the management of benign liver tumours. J Hepatol. 2016;65(2):386-98.
10. Venturi A, Piscaglia F, Vidili G, Flori S, Righini R, Golfieri R, et al. Diagnosis and management of hepatic focal nodular hyperplasia. J Ultrasound. 2007;10(3):116-27.
11. Buscarini E, Danesino C, Plauchu H, de Fazio C, Olivieri C, Brambilla G, et al. High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary haemorrhagic telangiectasia. Ultrasound Med Biol. 2004;30(9):1089-97.
12. Vilgrain V, Uzan F, Brancatelli G, Federle MP, Zappa M, Menu Y. Prevalence of hepatic hemangioma in patients with focal nodular hyperplasia: MR imaging analysis. Radiology. 2003;229(1):75-9.
13. Rebouissou S, Couchy G, Libbrecht L, Balabaud C, Imbeaud S, Auffray C, et al. The beta-catenin pathway is activated in focal nodular hyperplasia but not in cirrhotic FNH-like nodules. J Hepatol. 2008;49(1):61-71.
14. Rebouissou S, Bioulac-Sage P, Zucman-Rossi J. Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. J Hepatol. 2008;48(1):163-70.
15. McCann CN, Penny SM. Focal Nodular Hyperplasia. JDMS. 2013;29(1):17-23.
16. Scalori A, Tavani A, Gallus S, La Vecchia C, Colombo M. Risk factors for focal nodular hyperplasia of the liver: an Italian case-control study. Am J Gastroenterol. 2002;97(9):2371-3.
17. Sumiyoshi M, Sakanaka M, Kimura Y. Chronic intake of a high-cholesterol diet resulted in hepatic steatosis, focal nodular hyperplasia and fibrosis in non-obese mice. Br J Nutr. 2010;103(3):378-85.
18. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy. J Hepatol. 2023;79(3):768-828.
19. Marrero JA, Ahn J, Reddy RK, American College, of Gastroenterology. ACG Clinical Guideline: The Diagnosis and Management of Focal Liver Lesions. Am J Gastroenterol. 2014;109(9):1328-47; quiz 1348.
20. Mounajjed T. Hepatocellular Adenoma and Focal Nodular Hyperplasia. Clin Liver Dis (Hoboken). 2021;17(4):244-8.
21. Hsee LC, McCall JL, Koea JB. Focal nodular hyperplasia: what are the indications for resection? HPB (Oxford). 2005;7(4):298-302.
22. Chen TC, Chou TB, Ng KF, Hsieh LL, Chou YH. Hepatocellular carcinoma associated with focal nodular hyperplasia. Report of a case with clonal analysis. Virchows Arch. 2001;438(4):408-411.
23. Kinoshita M, Takemura S, Tanaka S, Hamano G, Ito T, Aota T, et al. Ruptured focal nodular hyperplasia observed during follow-up: a case report. Surg Case Rep. 2017;3(1):44-4.
24. Yajima D, Kondo F, Nakatani Y, Saitoh H, Hayakawa M, Sato Y, et al. A fatal case of subcapsular liver haemorrhage in late pregnancy: a review of haemorrhages caused by hepatocellular hyperplastic nodules. J Forensic Sci. 2013;58 (Suppl 1):253.
25. Si Y, Sun B, Zhao T, Xiao K, Zhao D, Huang Y. Case Report: Rare Acute Abdomen: Focal Nodular Hyperplasia With Spontaneous Rupture. Front Oncol. 2022;12:873338.
26. Jung J, Hwang S, Kim K, Ahn C, Moon D, Ha T, et al. Surgical indications for focal nodular hyperplasia of the liver: Single-center experience of 48 adult cases. Ann Hepatobiliary Pancreat Surg. 2019;23(1):8-12.
27. La Vecchia, C., & Tavani, A. Female hormones and benign liver tumours. Dig Liver Dis. 2006;38(8):535-6.
28. Imtiaz S. Imaging focal nodular hyperplasia. Appl Radiol. 2017;46(2):26-30.
29. Hartleb M, Gutkowski K, Milkiewicz P. Nodular regenerative hyperplasia: evolving concepts on underdiagnosed cause of portal hypertension. World J Gastroenterol. 2011;17(11):1400-9.

Corresponding author:

Dr. Eliezer Zahra Bianco, Department of Gastroenterology, Mater Dei Hospital, Msida, Malta
E-mail: eliezer.zahra-bianco@gov.mt