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Hepatobiliary Conditions

Management of focal nodular hyperplasia of the liver: Experience of 50 pediatric patients in a tertiary center

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ABSTRACT

Background: Focal nodular hyperplasia (FNH) is a rare benign hepatic lesion in children. No management guidelines for pediatric population exist because of limited evidence.
Objective: To review the experience of a large tertiary liver center, providing additional clinical data to help formulate management guidelines for FNH in the pediatric population.
Methods: We analyzed data of children <18 years diagnosed with FNH from 1996 to 2018 at our hospital, detailing management and long-term clinical outcome.
Results: 50 patients were identified. The median age was 10 years old (range 0.75–15.5 years old). The mean diameter of FNH was 5.9 cm (±3.1 cm). 10 patients had multiple lesions.
First-line management: watchful waiting with serial checks ($n = 37$), surgery ($n = 13$). Of the watchful waiting patients, 10 required eventual second-line surgery.
After a median follow-up of 4.7 years (range 0.5–20 years), 46 patients were asymptomatic, with no significant difference in clinical outcome ($p = 0.962$) between the two first-line management approaches.
Lesions demonstrated growth in 13 cases: 5 of these required second-line surgery. In these patients, there was no significant difference in clinical outcome ($p = 0.188$) compared to nonoperative patients.
Considering all surgically treated patients, there was no significant difference between first-line and second-line surgery for clinical outcome ($p = 0.846$), hospital stay ($p = 0.410$), complications ($p = 0.510$) and severe complications ($p = 0.385$).
Conclusions: Our data support the hypothesis that watchful waiting is a safe initial approach to pediatric FNH management in patients with no major symptoms or complications. Surgery should be reserved for patients with diagnostic doubt, persistent symptoms and/or biological or significant anatomical abnormalities. FNH growth alone should not be considered as an indication for surgery.
Type of study: Therapeutic study.
Level of evidence: Level III.

Focal nodular hyperplasia (FNH) is a well-circumscribed, non-neoplastic lesion characterized by benign appearing hepatocytes with vascular anomalies and ductal proliferation [1,2]. Pediatric cases are rare, accounting for 15% of all reported cases of FNH and representing 2%–7% of all pediatric hepatic tumors and 0.02% of all pediatric solid tumors [2–4]. The etiology is unknown [2,5,6], but several theories have been suggested, for example: vascularization by an anomalous artery, reactive hyperplasia after hepatocellular injury induced by vasculitis, or aberrant increased blood flow [5]. Risk factors include history of malignancy and chemotherapy [1–3,5,7,8] as well as vascular malformations [1,2,5,8–11]. There is a female predominance, as seen in adults [1,2,6,8,12] and most patients are asymptomatic at diagnosis [1–3,8]. Common imaging features include an isoechoic nodule, with hypervascularity on ultrasound (US), and intense arterial-enhancement, becoming isodense/isointense on portal venous or delayed phase imaging, on contrast-enhanced CT and MRI [13]. A central scar, a characteristic feature of FNH, can be absent in small lesions [1,6,13].

Currently, no specific management guidelines for FNH in pediatric patients exist [1–5,8,14]. This is primarily owing to the fact that this tumor is rare and the largest series of patients published to date included altogether only a few hundred patients. No prospective or retrospective studies have been published that address the clinical management of these tumors and therefore centers rely on expert

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consensus and experience. In adults, FNH is often an incidental finding, asymptomatic and considered a stable and benign lesion with no follow-up recommended in established guidelines [6]. These guidelines do not apply to the pediatric population, in part because we know that FNH lesions tend to grow, causing diagnostic uncertainty and anxiety, and because children are more likely to be symptomatic [4,8].

The aim of this study was to review the experience of a large tertiary liver center and to provide additional clinical management and outcome data in order to help formulate management guidelines for this lesion in the pediatric population.

1. Methods

A retrospective analysis of all patients <18 years old referred to our center's pediatric general and hepatobiliary surgery service between 1996 and 2018 with a liver tumor suspicious for FNH was undertaken. These were comprised of local, national and internationally referred patients. Inclusion criteria: children with a final histological diagnosis of FNH, confirmed by an expert pathologist in pediatric liver disease, or children with radiological diagnostic features of FNH confirmed by a radiologist with expertise in pediatric liver disease, where histology was not available or not required owing to typical imaging features and no clinical or biological red flags. Clinical, biological, radiological and surgical features were analyzed, as well as first-line and second-line management and follow up. Owing to the benign nature of the lesion, the clinical marker used to determine management outcome was persistence of clinical symptoms at the end of the follow-up.

In the absence of previous definitions in the literature, we defined an arbitrary measure of growth of the lesion during the follow-up period. We defined "growth" as an increase in the maximal diameter of the lesion by at least 50%, or an increase in the number of lesions.

Terminology for liver anatomy and hepatectomies follows the Bismuth 2012 classification [15]. Surgical complications were evaluated following the Clavien–Dindo classification [16].

We reviewed articles published in English from January 2008 to January 2019 with key words: focal nodular hyperplasia, pediatric, child, children.

Categorical variables are reported as absolute and relative frequencies (%). For continuous variables a Kolmogorov–Smirnov test for normality was performed. Normal distribution continuous variables are reported as mean and standard deviation, nonnormal distribution variables as median and range. Groups were compared using the Chi-square exact test for categorical variables. For non-normal distribution variables, differences between groups were established with a non-parametric test, U Mann–Whitney test. For normal distribution variables, differences between groups were established with a T student test. Statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY).

2. Results

2.1. Population and diagnosis (Table 1)

78 patients were initially identified. 28 were excluded: 22 with insufficient data, 3 had had management of a hepatic vascular malformation and were 3 lost to follow-up after diagnosis. The study population was comprised of 50 patients including 37 (74%) females. The median age was 10 years old (range 0.75–15.5 years old). Common comorbidities included vascular anomalies ($n = 10$), malignancy with chemotherapy ($n = 4$), and sickle cell disease ($n = 3$). Other isolated comorbidities were biliary atresia, liver transplantation, type 1 diabetes, Hashimoto thyroiditis, polycystic ovary disease, complex cardiac malformations, Von Willebrand's disease, membranoproliferative glomerulonephritis, and esophageal atresia.

For 27 (54%) patients FNH was incidentally found on imaging during the management of other clinical conditions. Twenty three (46%) patients were symptomatic at diagnosis: abdominal pain ($n = 15$), palpable mass ($n = 5$), vomiting ($n = 2$), and anorexia ($n = 1$). Thirty two patients had normal liver function tests at diagnosis. Two (4%) patients had a raised AFP at diagnosis. One was a 5 year old boy (AFP = 139 μg/L) with history of resected hepatoblastoma and chemotherapy. This patient developed a nodule of indeterminate nature on imaging and had a raised AFP. This was resected and was histologically confirmed as FNH. No recurrence of hepatoblastoma was documented in this patient. The second patient was an 11 year old girl with history of surgical portosystemic shunt formation for portal vein obstruction (AFP stable at between 22 μg/L and 25 μg/L from diagnosis and during 8.5 years of follow-up for FNH).

Table 1
Population and diagnosis.

Age (years)		10[a] (0.75–15.5)[b]
Sex	Female	37 (74%)
	Male	13 (26%)
History	Vascular anomalies	10 (20%)
	Malignancy on CHT	4 (8%)
	Sickle Cell Disease	3 (6%)
Symptoms		23 (46%)
Presentation	Incidental diagnosis	27 (54%)
	Abdominal pain	15 (30%)
	Palpable mass	5 (10%)
	Vomiting	2 (4%)
	Anorexia	1 (2%)
D_{max} (cm)		5.9[c] (±3.1)[d]
Location	Right Liver	25 (50%)
	Left Liver	28 (56%)
	Segment 1	6 (12%)
Number of lesions	1	40 (80%)
	2	3 (6%)
	≥3	7 (14%)
Normal LFT		32 (64%)
Biopsy	Needle	11 (22%)
	Surgical	1 (2%)
Follow up (years)		4.7[a] (0.5–20)[b]

CHT = chemotherapy, D_{max} = maximal diameter of biggest FNH, LFT = Liver function tests.
[a] Median.
[b] Range.
[c] Mean.
[d] Standard deviation.

In order to achieve initial radiological diagnosis, US was performed in 49 (98%) patients, CT in 20 (40%), MRI in 19 (38%) and arteriography in 4 (8%). Histological confirmation was required in 12 (24%) patients, to rule out a malignancy or resolve diagnostic uncertainty. Confirmation was achieved using US-guided needle biopsy ($n = 11$) or surgical biopsy ($n = 1$). The surgical biopsy was performed to exclude malignancy before surgical planning owing to inaccessibility of the lesion with conventional image-guided biopsy. Patients that needed biopsy for diagnosis confirmation had significantly worse clinical outcome at the end of the follow-up ($p = 0.005$).

Thirty (60%) patients had a final histological diagnosis of FNH, while 20 patients were diagnosed by imaging alone. No biopsy or resection was needed for diagnosis or management of this group of imaging-only patients, and they required no further intervention. No diagnostic error occurred in the imaging only group or in the remaining population, using lesion stability and lack of adverse findings as a marker of outcome in the follow-up period i.e. malignant transformation, metastasis, or rupture.

The mean maximal diameter of the largest FNH lesion at diagnosis was 5.9 cm (±3.1 cm). Patients with FNH of at least of 2.5 cm maximal diameter are more likely to have abnormal liver function tests at diagnosis ($p = 0.035$). FNH of 5.5 cm or greater maximal diameter at diagnosis was more often symptomatic at diagnosis ($p = 0.047$) and at the end of the follow-up ($p = 0.037$). Female patients were found to have significantly more lesions of at least 3.5 cm maximal diameter than males ($p = 0.030$).

Ten (20%) patients had multiple FNHs, of which 7 patients had at least three lesions. No significant difference in presence of symptoms was found between patients with single or multiple lesions at diagnosis ($p = 0.065$) or at the end of follow-up ($p = 0.794$). Male patients developed significantly more multiple lesions (at least 3) than females ($p = 0.043$).

Right liver was involved in 25 (50%) patients, left liver in 28 (56%), left lobe in 20 (40%), segment 4 in 14 (28%), and segment 1 in 6 (12%). When the right liver was involved, patients were more often symptomatic at diagnosis ($p = 0.047$). When segment 4 was involved, patients were more likely to have abnormal liver function test at diagnosis ($p = 0.046$). Segment 1 was more often involved in male patients than in females ($p = 0.015$).

2.2. Management (Fig. 1)

Two first-line management options were used: watchful waiting with serial checks and upfront surgery.

Thirty seven (74%) patients underwent watchful waiting as first-line management (Table 2). The choice of watchful waiting as first-line management was significantly higher when the right liver was affected ($p = 0.004$). The median length of watchful waiting of 3.5 years (range 0.5–20 years). Ten of these patients required second-line surgery with no patient developing a contraindication to this in the follow-up period. The mean time between watchful waiting and second-line surgery was 3.1 years (±2.6 years). Indication for second-line surgery included lesion growth ($n = 5$), persistent symptoms ($n = 3$: 2 abdominal pain, 1 mild dyspnea) and patent portosystemic shunts ($n = 2$). Surgical procedures included nonanatomical hepatectomies or tumorectomy ($n = 6$), trisegmentectomy ($n = 1$), bisegmentectomy ($n = 1$), segmentectomy ($n = 1$), and surgical shunt closure ($n = 1$). The patient that needed surgical shunt closure had diagnosis of a portosystemic shunt made during the watchful waiting period for FNH. The indication for surgical shunt closure was the growth of the FNH from 2 cm to 8 cm in 8 years of follow-up: she had already had a failed attempt at interventional closure. She showed an almost complete regression of the FNH after the surgery.

Table 2
Watchful waiting details.

Watchful waiting length (years)		3.5[a] (0.5–20)[b]
Second-line surgery		10 (27%)
Time from watchful waiting to surgery (years)		3.1[c] (±2.6)[d]
Indication	Growth	5 (50%)
	Symptoms	3 (30%)
	Portosystemic shunt	2 (20%)
D_{max} evolution	Growth in size ($D_{max} > +50\%$) and/or number	13 (35%)

D_{max} = maximal diameter of major FNH lesion.
[a] Median.
[b] Range.
[c] Mean.
[d] Standard deviation.

Six patients developed complications: 3 type I, 1 type II, 1 type IIIb, and 1 type IVa. The type IIIb complication was a biloma after liver resection requiring a second laparotomy. The type IVa complication was respiratory distress requiring intubation. The mean hospital stay for surgery was 11.5 days (±1.8 days). At the end of the follow-up, in the watchful waiting patients there was no significant difference in clinical outcome ($p = 0.798$) compared to the surgically treated patients. In this cohort, lesions demonstrated growth in 13 patients: 5 of these underwent a second-line surgery.

Growth was more often seen in patients with multiple FNH at diagnosis ($p = 0.001$) and by patients with a history of vascular anomalies ($p = 0.008$). At the end of follow-up, in watchful waiting patients there was no significant difference in clinical outcome ($p = 0.946$) between those patients with lesion growth and those without. At the end of follow-up, in patients with lesion growth, there was no significant difference in clinical outcome ($p = 0.188$) between those who were surgically treated and those who were not.

Thirteen (26%) patients had surgery as first-line management (Table 3). The decision to proceed to first-line surgery was significantly higher when FNH was at least of 6.5 cm maximal diameter ($p = 0.033$) and when there was left liver involvement ($p = 0.016$), especially if in the left lobe ($p = 0.002$). Indications for first-line surgery included: symptoms ($n = 5$: 4 abdominal pain, 1 discomfort and anorexia), lesion dimension ($n = 4$), portosystemic shunt ($n = 2$), and diagnostic

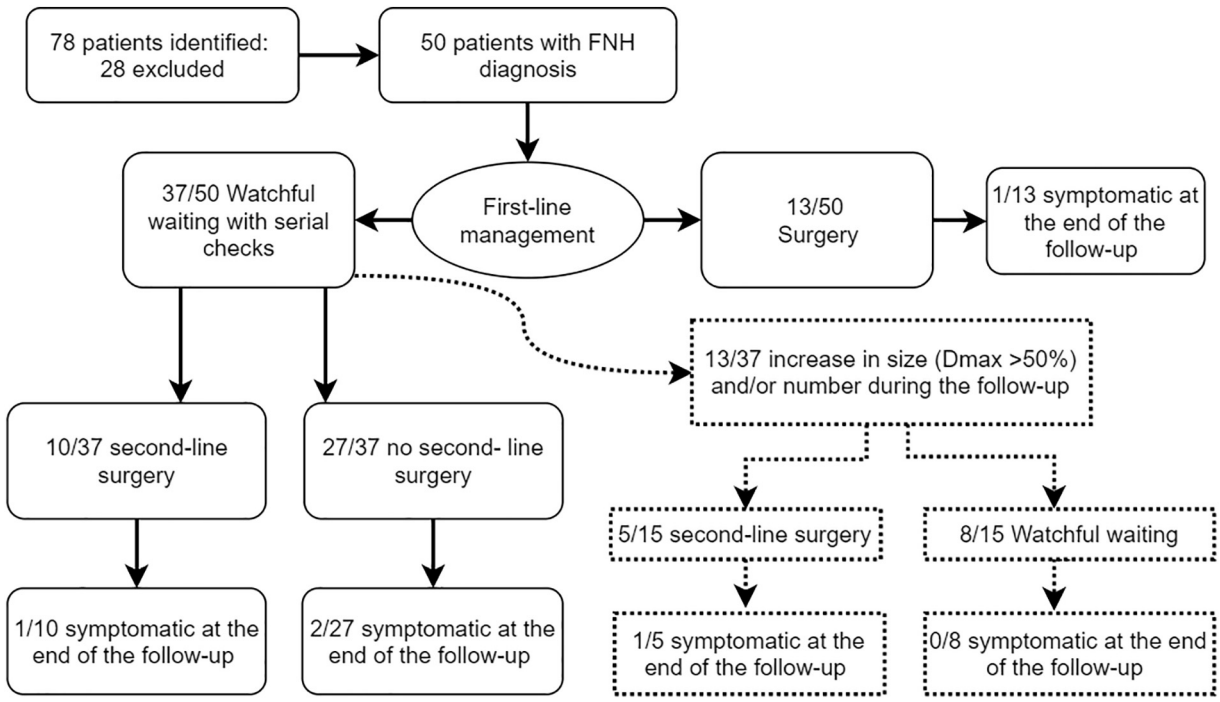

Fig. 1. Study overview: outcomes in the various groups of the study population. D_{max} = maximal diameter of biggest FNH.

Table 3
Surgery details.

		First-line	Second-line	Total
Patients		13	10	23
Indication	Symptoms	5	3	8
	Growth	-	5	5
	Dimension	4	-	4
	Portosystemic shunt	2	2	4
	Diagnostic problems	2	-	2
Complications		6 (46.1%)	6 (60%)	12 (52.1%)
Severe complications (≥IIIA)		1 (7.6%)	2 (20%)	3 (13%)
Type	I	4	3	7
	II	1	1	2
	IIIA	-	-	-
	IIIB	-	1	1
	IVA	1	1	2
	IVB	-	-	-
	V	-	-	-
Need for blood transfusion		2 (15.3%)	6 (60%)	8 (34.7%)
Need for vascular exclusion		5 (38.4%)	8 (80%)	13 (56.5%)
Hospital stay (days)		10.2[a] (±3.6)[b]	11.5[a] (±3.0)[b]	10.7[a] (±3.5)[b]
Symptoms at the end follow-up		1 (7.6%)	1 (10%)	2 (8.6%)

D_{max} = maximal diameter of biggest FNH.
[a] Mean.
[b] Standard deviation.

uncertainty ($n = 2$). Surgical procedures: non-anatomical hepatectomy or tumorectomy ($n = 5$), left lobectomy ($n = 4$), left hepatectomy ($n = 1$), segmentectomy ($n = 1$), bisegmentectomy ($n = 1$), and trisegmentectomy ($n = 1$). Six patients developed complications: 4 type I, 1 type II and 1 type IVA. The type IVa complication was respiratory distress requiring intubation. The mean hospital stay for surgery was 10.2 days (±4.4 days).

All considering, 23 surgical procedures were performed: 13 first-line and 10 second-line. In surgically treated patients, there was no significant difference between first-line and second-line treatment in terms of complications ($p = 0.510$), severe complications (≥IIIa) ($p = 0.385$), hospital stay ($p = 0.410$) or clinical outcome ($p = 0.846$). Instead first-line surgery required fewer transfusions ($p = 0.026$) and less need for vascular exclusion ($p = 0.046$) when compared to second-line surgery. When right liver was involved by FNH, surgical procedures presented significantly more complications ($p = 0.013$), more severe complications (≥IIIa) ($p = 0.011$), more need for vascular exclusion ($p = 0.029$), and increased requirement for blood transfusion ($p = 0.001$). When the left lobe was involved, surgical procedures presented significantly fewer severe complications (≥IIIa) ($p = 0.050$), less need for vascular exclusion ($p = 0.019$), and less need for blood transfusion ($p = 0.001$).

2.3. Follow-up and outcome (Fig. 1)

The median follow-up was 4.7 years (range 0.5–20 years). Patients were followed-up until released to adult centers at 16–18 years old. No patient developed rupture or hemorrhage of their FNH. No malignant transformation of FNH occurred. No diagnostic error occurred to our knowledge. No deaths related to FNH or management occurred. No patients developed a contraindication to surgery during the follow-up period.

At the end of the follow-up period, 46 patients (92%) were asymptomatic, with no significant difference for clinical outcome ($p = 0.962$) in the two first-line management groups. Of the 4 patients still symptomatic at the end of the follow-up, 2 had persistent mild chronic abdominal pain, 1 persistent dyspnea and 1 persistent vomiting. The patient with persistent dyspnea had an uncommon multiple and progressive variety of FNH, requiring surgery (left lobectomy extended to segment 1) as second-line treatment after watchful waiting. This was not successful and an embolization of the FNH as third-line treatment was performed. Despite the radiological success of this procedure, symptoms persisted. For the 3 other symptomatic patients the symptoms appear unlikely to be related to FNH.

3. Discussion

FHN is a clinically indolent lesion for which watchful waiting has often been suggested in the pediatric population, but with no solid evidence base [1,2,5,7]. Serious complications of FNH are very uncommon and rupture or hemorrhage is extremely rare. Only 10 documented cases of hemorrhage caused by FNH are described in the literature [17], with the youngest patient being 18 years old. No ruptures or hemorrhage occurred in this study.

Progressively increasing size of FNH leading to compression of major structures is extremely rare: only 7 are reported in the literature [18–23], of which only two are pediatric cases [22,23]. One case of progressive and multiple FNH occurred in our population, requiring listing to transplantation in an adult center after failed watchful waiting (4 years), second-line surgery, and third-line vascular embolization, for persistent dyspnea. Only 1 case of recurrence in an adult patient of FNH after resection has been described in literature [22]. No recurrences are described for pediatric patients or in our population.

Currently, no management guidelines for FNH in pediatric patients exist, owing to a lack of evidence base. Between January 2008 to January 2019, 307 cases of FNH in pediatric patients are reported in the literature. Published work has until now been more focused on diagnostic or clinical features rather than on management [7,13,24–29]. Most of them have small original sample sizes [3,4,14,25–27,29–43], others have limited standardization or follow-up [3,8], and some limit the analysis to one or few aspects of management or to a limited population [7,25,29,31,32,34,35,37,43]. This series is focused on long-term outcomes of various management options, with a median follow-up length of 4.7 years. This is the first series focused with a large original sample (second largest ever [8]), a standardized evaluation of FNH's features at diagnosis and during the follow-up, and a standardized analysis of management, including surgical procedures, their complications and outcome.

In recent years, the management strategy for FNH in pediatric patients has evolved. Some years ago, surgery was considered the best first-line option for the pediatric population [3,8,43]. Then, despite no major published evidence, watchful waiting management started to take its place [4,7,8,14,31,37,44]. This was likely owing to the influence of the more conservative approach used in adults [6]. Indeed, in the adult population FNH is considered a stable lesion, so no follow-up is recommend [6]. This was certainly our experience and reflects the greater use of surgery in the earlier part of our study. Part of the reason that 1996 was used as our cutoff was because it was from this time that the approach to these lesions at our institute began to change towards a more conservative approach. This has continued and now patients only very uncommonly undergo primary surgery.

However, in practice, adult guidelines appear to be too optimistic for the pediatric population as children are more likely to be symptomatic (46% in the present series) and often have severe comorbidities to deal with. Furthermore, in pediatric cases of FNH, growth of the lesion is common (35% in the present series), which creates anxiety within the patient, their family and the clinicians.

Management is based on confidence in the diagnosis, which can be difficult because of the rarity of FNH in the pediatric population, owing to clinical and imaging overlap between differential diagnoses with lesions such as fibrolamellar hepatocellular carcinoma, adenoma, regenerative nodules, hemangioma and other malignancies [5].

Currently, there is limited experience in children of using transarterial vascular embolization to manage FNH, which other authors [36,45] have reported as having good outcomes, and which we have used in our institution infrequently but with good effect. A further minimally invasive approach, percutaneous ablation, has been used successfully in adults with benign liver lesions who were not surgical candidates [46], but to date, no

reports of this technique in the pediatric population have been published in the literature.

Therefore, when invasive management is required, given the real risk of such surgeries, we suggest that this is undertaken at experienced tertiary centers, in order to minimize complications in the short and long term.

Here we propose recommendations for management of pediatric FNH, based on our data and on the recent literature. Our series shows three main points.

Firstly, there is no significant difference in clinical outcome ($p = 0.962$) between watchful waiting and surgery as first-line management.

Secondly, in surgically treated patients, there was no significant difference between first-line and second-line treatment in terms of clinical outcome, hospital stay, complications or severe complications (≥IIIa). However, first-line surgery showed significantly less needing for transfusion or vascular exclusion than second-line surgery, reflecting the fact that it is more often the complicated cases with more difficult surgical access that are observed in the first instance, and only operated when symptoms are particularly bad. Naturally, this leads to a selection bias for cases that will require more complex intervention and have more complications for example, centrally-located tumors.

Thirdly, in watchful waiting patients that demonstrated a growth of FNH, there was no significant difference in clinical outcome ($p = 0.188$) between surgically treated and nonsurgically treated patients. Watchful waiting has no significant increased morbidity or mortality risk compared to surgery. Surgery was overall a safe treatment. However, despite being in a tertiary center specialized in pediatric hepatobiliary surgery and pediatric liver transplantation, 52.1% of procedures had some complications, of which 13% were severe (≥IIIa). Therefore, surgery, because of its risks, should be reserved for patients with persistent symptoms or complications. It should be recognized that despite successful surgery, 4 of our patient cohort continued to have symptoms, which raise the question of whether the FNH was truly the cause of symptoms in the first place.

Using our experience and data from this cohort of patients and in line with expert consensus, we provide a multidisciplinary management algorithm (Fig. 2) to help physicians, radiologists and surgeons outside the tertiary centers to deal with this rare lesion in pediatric population. The aim is also to stimulate debate on pediatric FNH management between members of tertiary centers. When there is a suspicion of FNH, based on clinical and/or radiological features, the diagnosis of FNH must be confirmed and the differential diagnoses excluded, especially with fibrolamellar carcinoma that is similar in appearance and

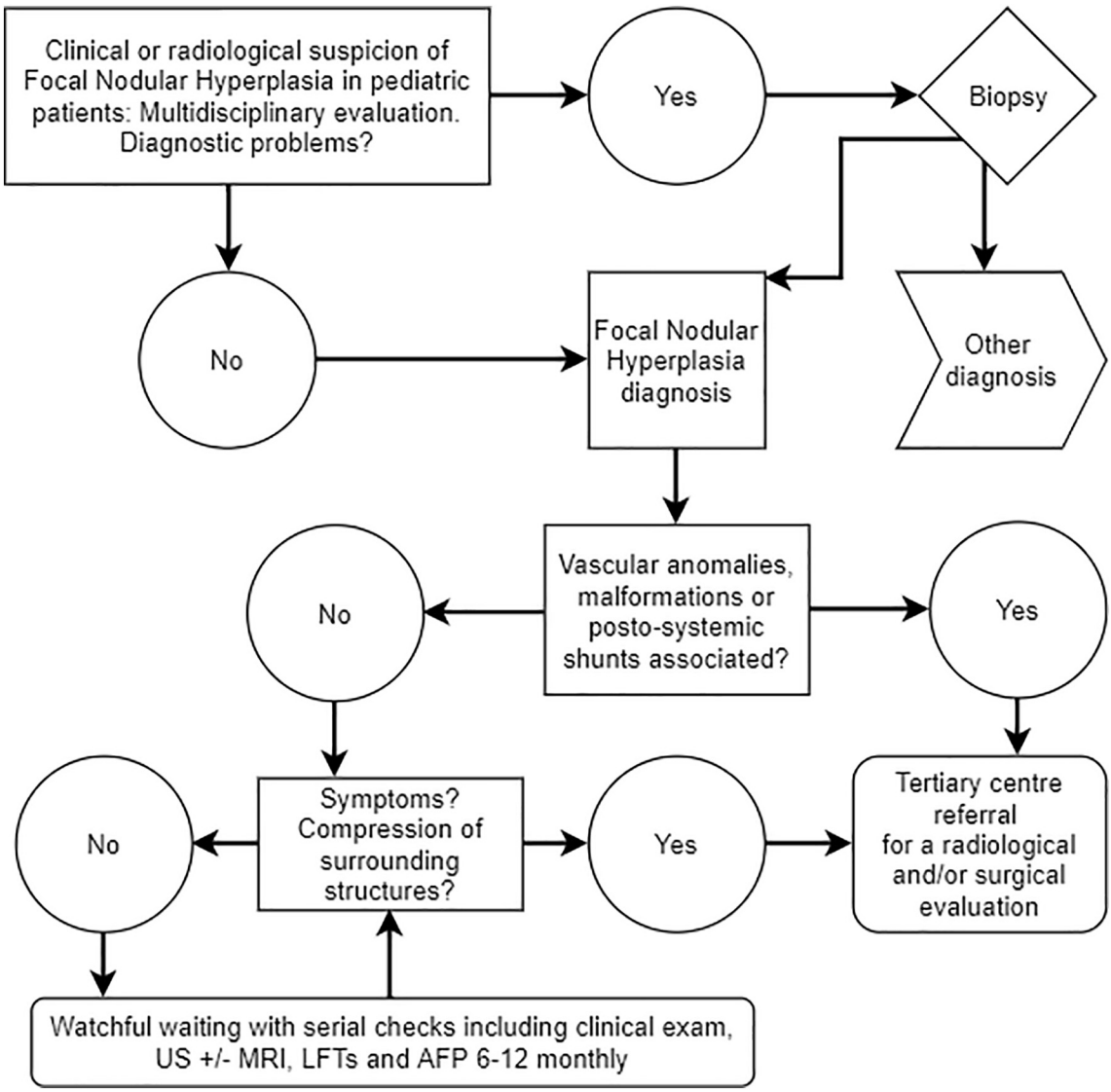

Fig. 2. Proposition of our protocol for management of Focal Nodular Hyperplasia in pediatric patients: Bicetre protocol. US = ultrasound, MRI = magnetic resonance imaging, LFTs = Liver function tests, AFP = alpha fetoprotein.

can affect patients in the same age range [5]. When radiological features confirm the diagnosis and neither clinical nor biological features put this in doubt, FNH diagnosis can be confidently established. When there are unclear or incongruent features, the diagnosis must be confirmed by histological examination. In this case a biopsy, preferably an US-guided needle biopsy, should be performed. Once the diagnosis is confirmed, the patient must be explored for comorbidities, especially for hepatic vascular anomalies or abnormal hepatic circulation as these conditions may require specific management.

In the absence of major symptoms or discomfort or compression of the hepatic and/or abdominal structures, watchful waiting management should be chosen. The watchful waiting approach is based on serial checks with clinical examination, liver US and/or MRI, liver function tests and AFP every 6 months for 2–4 years, and then reduced to once per 12 months, depending on clinician preference and stability of the biological markers and/or symptoms. If the patient, at diagnosis or at any time during the watchful waiting period, presents major symptoms or complications, they should be referred to a tertiary center for radiological and surgical evaluation. An isolated change in the size of the lesion should not be considered as an indication for surgery, if it does not cause symptoms or compression of surrounding structures.

In our institution's experience on difficult localizations, the standard approach for surgical resection remains unchanged. Among the possible liver localizations, left lobe resection is less technically challenging and therefore lesions can be observed for longer without fear that rapid growth will render the surgical procedure more difficult. However, for a more central or right-sided localization, the tumor may become even more difficult to remove if left to grow. Therefore, the benefit to risk ratio should be greater when deciding to operate on these children.

Owing to the growth of the child, FNH lesions can appear to grow but, usually, do not extend to other liver segments. Therefore, tumorectomy can be proposed for FNH removal and anatomical resection of the segment involved is not required, as would be the case in malignancy.

In cases of rapid growth e.g. 30% in 6 months, we suggest that surgery could be proposed without delay in symptom-free patients in order to minimize the chance of a more complex surgery in the future. This is extrapolated from our experience with patients with tumors such as hepatoblastoma and is not specifically drawn from our FNH study data.

From the analysis of the recent literature [1–6] we found no data indicating a relationship between puberty and FNH's development, growth or multiplication. In the present study, the puberty issue has not been discussed for lack of data. Owing to the retrospective nature of the present study and the characteristics our clinical records, it is not possible to define when puberty started for almost all the patients and so study its effect on FNH's evolution. This would be something to consider in any further prospective study.

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4. Limitations

The strength of our data must be qualified by the limited retrospective nature of this study. Growth of the lesion was measured in only one plane (longest diameter) owing to the variation in available imaging across the cohort. We acknowledge that more robust measures, such as lesion:liver volume would be more useful for comparison across cohorts, but data such as slice thickness, slice interval and multiplanar views/reconstructions were not always available to our radiology colleagues at the time of our analysis. In addition, patients who had initial imaging in our hospital but who were followed up in centers outside of our own, did not always have their imaging on our local imaging system for review. Therefore, subsequent growth was calculated from reports or clinic notes, comparing the reported size and calculating the difference from baseline.

Furthermore, owing to evolving expert opinion over the study period, it is clear that resection was more likely to occur in the earlier part of the study than more recently. Therefore, some of the surgeries performed in the past, would now not be indicated by our own proposed standards, but have helped us to write this article and will aid others in learning from our experience in this rare tumor type.

It should be noted that hepatobiliary-specific contrast is not available in our institution and therefore the biopsy rate (12/50 patients) may be higher than in other similar institutions. Also, with the recent increase in availability of contrast-enhanced US, biopsy rates are likely to fall further in the future.

Further prospective, multicenter studies are required to validate these data and approach owing to the rarity of this lesion.

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