

Focal nodular hyperplasia in children, adolescents, and young adults

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Abstract

Background Focal nodular hyperplasia (FNH) is a benign hepatic tumor that is rare in children. In order to understand whether there are differences in the etiology or appearance of FNH in children, we analyzed the clinical information and imaging of pathologically proven cases.

Materials and methods A pathology database was used to identify all cases of FNH diagnosed at our institution. Each patient's imaging was evaluated for the characteristics of FNH lesions. Clinical information was obtained on each patient.

Results Thirteen patients with FNH were identified (7 male/6 female, mean age 14.3 years, range 1–27 years). Seven patients (5 male/2 female) had a remote history of childhood malignancy. The time interval between the diagnoses of malignancy and FNH ranged from 9 to 27 years (mean 14.4 years). On imaging, all seven cancer survivors had multiple liver lesions. In the remaining six patients (2 male/4 female), there was no history of malignancy and all but one of these patients had a solitary FNH.

Conclusion Half of the patients with FNH in this study were long-term cancer survivors and each of these patients had multiple masses. Recognizing the features of FNH will aid in diagnosis and appropriate management.

Keywords FNH · Hepatic tumor · Liver tumor · Children · Adolescents · Focal nodular hyperplasia

Introduction

Focal nodular hyperplasia (FNH) is a benign hepatic tumor characterized by hepatocyte hyperplasia and a central stellate scar. It is an uncommon entity in children, accounting for only 2% of pediatric liver tumors [1]. Often, FNH appears as a solitary liver mass in a patient imaged for other reasons. These incidental lesions are eight times more common in females and usually have a characteristic imaging appearance [2, 3].

Multiple studies have shown an increased incidence of FNH in long-term survivors of childhood malignancies or hematopoietic stem cell transplant [4–15]. It is thought that FNH is a complication of chemotherapy or radiation therapy in these patients. The purpose of this study is to evaluate the etiology and appearance of FNH in children.

Materials and methods

Following IRB review and approval, a retrospective study was performed. A pathology database was queried to identify all patients with pathology-proven FNH at our institution between 1998 and 2010. After the patients were identified, their medical records were searched for demographic information (age, sex), clinical history and oral contraceptive use. If the patient's clinical history included a malignancy, additional clinical information was obtained, including the type of malignancy, the type of chemotherapy or radiation therapy used in the treatment of the malignancy, and the presence or absence of veno-occlusive disease.

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Table 1 Clinical characteristics and imaging findings of FNH in patients with a remote history of malignancy

Pt	Age at diagnosis of cancer (years)	Age at diagnosis of FNH (years)	Years between cancer diagnosis and FNH	Sex	Tumor	# of lesions	Max diameter (cm)	Chemotherapy	Rad	VOD	Modality	Imaging characteristics	Central scar?	Hepatic lesion at diagnosis?
1	<1 year	27	27	M	Neuroblastoma	8	2.3	Cyclophosphamide Dacarbazine Vincristine	Y	N	MRI	T1-W = slightly hypo to iso T2-W = hyper Contrast = enhances early and stays hyperintense	N	N
2	4	13	9	M	Medulloblastoma	3	3.3	Cisplatin Cyclophosphamide Etoposide Vincristine	Y	N	MRI	T1-W = hypo to iso T2-W = slightly hyper Contrast = enhances early fades with delayed images	N	N
3	<1 year	15	15	M	Hepatoblastoma	7	2.5	Pre-stem cell rescue: Carboplatin Thiotepa Doxorubicin Cisplatin	Y	N	MRI	T1-W = hypo T2-W = hyper Contrast = enhances early	N	Y
4	1	10	9	M	Medulloblastoma	2	2.3	Cisplatin Cyclophosphamide Vincristine	Y	N	CT	Noncontrast = hypo Contrast = enhances in the arterial phase	N	N
5	3	15	12	M	Neuroblastoma	3	1.5	Pre-stem cell transplant: Carboplatin Etoposide Melphalan Doxorubicin Cisplatin Cyclophosphamide	Y	N	MRI	T1-W = hypo T2-W = hyper Contrast = enhances early fades with delayed images	N	N
								Pre-stem cell transplant: Carboplatin Etoposide Melphalan Etoposide						

6	2	18	F	Neuroblastoma	5	5.1	Cisplatin Cyclophosphamide Doxorubicin Etoposide Pre-stem cell transplant: Cisplatin Doxorubicin Etoposide L-phenylalanine mustard	Y	N	MRI, CT	T1-W = hypo T2-W = hyper Contrast = enhances early Noncontrast = hyper (fatty background liver)	N	N
7	5	11	F	Wilms tumor	4	4.3	Doxorubicin Cyclophosphamide Daunomycin Etoposide Vincristine	Y	N	MRI	T1-W = iso T2-W = iso Contrast = enhances early fades with delayed images	Y	N

The radiology imaging database was then used to find all CTs and MRIs from patients identified through the pathology database query. The imaging studies were evaluated by one board-certified pediatric radiologist and the following information was recorded: imaging characteristics of the FNH, number of lesions, size of the largest lesion and the presence or absence of a central scar.

Results

Thirteen patients were identified through the pathology database as having FNH. All had cross-sectional imaging before tumor resection or biopsy. The 13 could be split into two distinct groups: those with a remote history of malignancy and those without malignancy.

Of the 13 patients diagnosed with FNH, 7 (5 male/2 female) had a remote history of malignancy. Malignancies included neuroblastoma in three patients, medulloblastoma in two, Wilms tumor in one and hepatoblastoma in one. The average age at diagnosis of FNH was 16.6 years (range 10–27 years). The average time interval between the diagnosis of the primary cancer and the pathological diagnosis of FNH was 14.4 years (range 9–27 years). All patients received both chemotherapy and radiation. The initial radiation therapy planning reports for five of the seven patients could not be located. Given the available notes as well as the location of the primary malignancy, it is thought that the radiation field included a portion of the liver in six of seven patients. Four patients received a stem cell transplant.

All patients with a history of malignancy had multiple FNH lesions within their liver (average 4.7; range 2–8). Only one child had an FNH with a central scar. The clinical and imaging characteristics of this group are presented in Table 1.

In the six children without a history of malignancy, there were four females and two males. The average age at diagnosis of FNH was 11.7 years (range 1–21 years). Only one patient was taking oral contraceptives; this patient also had a diagnosis of Turner syndrome. Five patients in this group had a solitary lesion and one had two large lesions. Three patients had an FNH with a central scar. The clinical and imaging characteristics of this group are presented in Table 2.

Discussion

FNH is a rare entity occurring in up to 0.02% of the general pediatric hospital population but in 0.45% of pediatric

Table 2 Clinical characteristics and imaging findings of FNH in patients with no history of malignancy

Pt	Age at diagnosis of FNH (years)	Sex	Symptoms/History	Oral contraceptive use	Number of lesions	Maximum diameter (cm)	Imaging modality	Imaging characteristics	Central scar
8	15	F	Anti-acne medication, abdominal pain	N	2	9.8	MRI, CT	T1-W = iso T2-W = hyper Contrast = enhances slightly, no arterial phase Contrast-enhanced CT = iso to hyper	N
9	3	F	Abdominal pain	N	1	9.1	CT	Contrast-enhanced CT (arterial) = hyper Contrast-enhanced CT (portal) = slightly hyper	Y
10	21	F	Tumer syndrome, incidental	Y	1	3.1	MRI	T1-W = iso T2-W = hyper Contrast = enhances	Y
11	16	M	Mononucleosis, hepatosplenomegaly, incidental	N/A	1	4.8	MRI	T1-W = iso T2-W = iso Contrast = iso on arterial phase; hypo on portal venous phase	N
12	14	F	Soccer injury, incidental	N	1	3.5	MRI	T1-W = slightly hypo T2-W = slightly hyper Contrast = enhances on arterial phase, iso with delay	Y
13	1	M	Pyloric stenosis, incidental	N/A	1	1.4	MRI	T1-W = iso T2-W = hyper Contrast = enhances on arterial phase, iso with delay	N

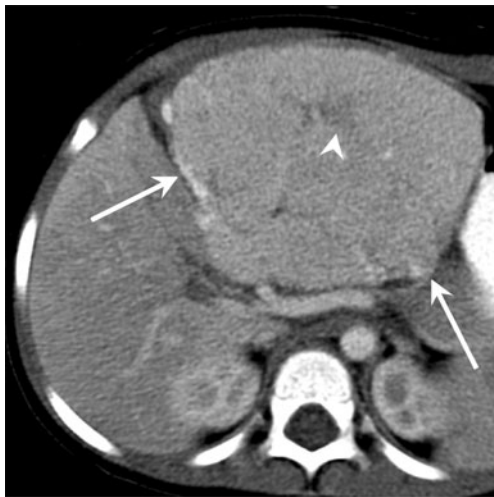


Fig. 1 Contrast-enhanced CT of the liver in the portal venous phase of imaging in a 3-year-old girl who presented with abdominal pain shows a large enhancing mass in the left lobe of the liver (arrows). A hypodense central stellate scar is also present (arrowhead)

patients who had been treated for a malignancy [4]. FNH typically presents as a solitary lesion, although multiple lesions have been described in approximately a quarter of adult patients [2].

The pathogenesis of FNH is unknown although the most accepted theory suggests that it is a result of congenital or acquired vascular abnormalities. It is speculated that the vascular abnormality leads to either arterial or portal venous thrombosis. Recanalization of the thrombosed vessel and subsequent reperfusion can then lead to hepatocyte proliferation and the development of FNH [15].

In children treated for a malignancy, it is thought that the chemotherapy or radiation therapy regimen leads to a vascular abnormality [4]. Prior studies have implicated the cytoreductive agents busulfan and melphalan as being

associated with FNH formation [4]. In this study, two of the seven patients with a malignancy were treated with melphalan. Chemotherapeutic agents that were more commonly used in patients in this study include cyclophosphamide (6 of 7 patients), cisplatin (5 of 7 patients), etoposide (5 of 7 patients), and vincristine (4 of 7 patients). It is possible that one or more of these agents also plays a role in the development of FNH. There has been no explanation as to why there is an increased incidence of FNH in patients treated for a pediatric malignancy but not in those treated for adult malignancies.

In adults, FNH is often diagnosed via imaging because of its characteristic appearance. Typically, the mass is less than 5 cm in diameter and has a central stellate scar (Fig. 1). On non-contrast-enhanced CT, an FNH is either hypo- or isodense to the surrounding liver (Fig. 2). A central scar is present in approximately 20% of lesions imaged via CT [16]. In the hepatic arterial phase of imaging, there is homogeneous and intense enhancement of the lesion with the exception of the central stellate scar (Fig. 2). In the portal venous phase, the mass becomes isodense as compared to the surrounding liver while the central scar might enhance [3].

On MRI, FNH is usually hypo- or isointense to the surrounding liver on T1-W images and iso- to slightly hyperintense on T2-W images (Fig. 3). A central scar is present in approximately 85% of lesions imaged via MRI [16]. The central scar is hyperintense to the liver and mass on T2-W images. The mass enhances homogeneously and intensely in the arterial phase of imaging (Fig. 3). As the liver enters the portal venous phase, the mass become more isointense to the surrounding liver (Fig. 3). The central scar retains contrast agent and enhances in the later phases of imaging [3].

In this study, the characteristics of FNH depended on the group. In the group of patients with a history of

Fig. 2 A 10-year-old boy with a history of medulloblastoma. **a** Noncontrast CT of the liver shows a slightly hypodense lesion in the right lobe of the liver (arrow). **b** Contrast-enhanced CT of the liver in the arterial phase of imaging shows homogeneous and intense enhancement of the liver mass (arrow)

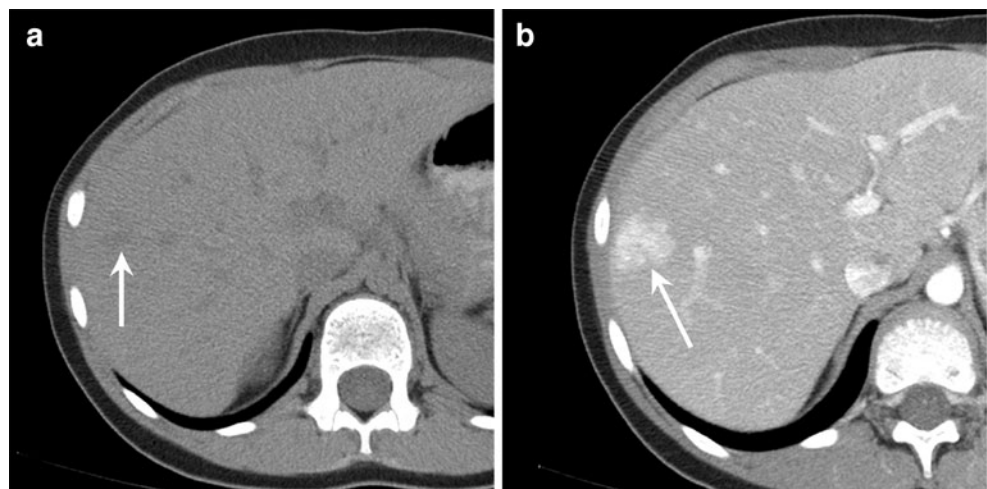
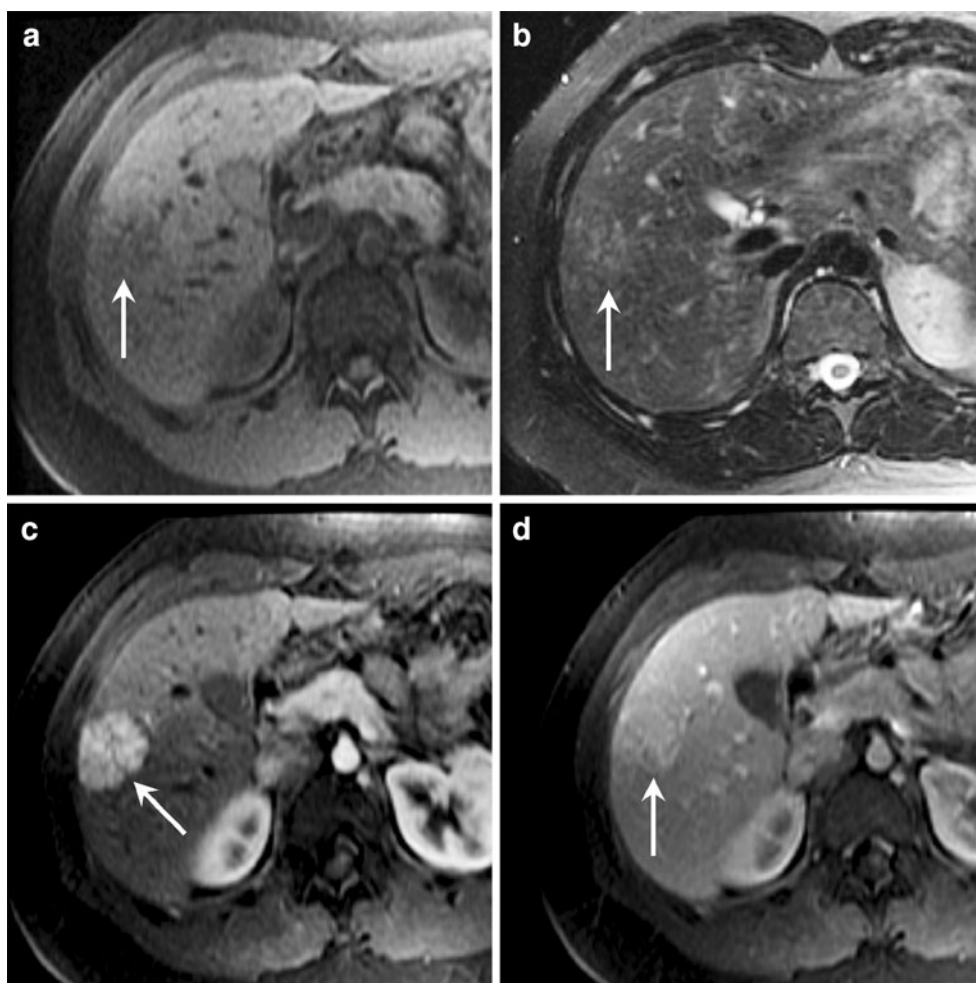


Fig. 3 A 14-year-old girl imaged after a soccer injury. **a** Axial T1-W MRI of the liver shows a slightly hypointense lesion in the right lobe of the liver (*arrow*). **b** Axial T2-W image of the liver shows a slightly hyperintense lesion (*arrow*). **c** Axial T1-W image after administration of gadolinium shows intense arterial phase enhancement of the mass (*arrow*). The tip of the arrow points to a central scar that is hypointense compared to the rest of the mass. **d** Axial T1-W post-contrast image in the portal venous phase of imaging shows that the mass is now only slightly enhancing compared to the background liver (*arrow*)



malignancy, all had multiple lesions (Fig. 4). In addition, FNH in this group was generally smaller (average diameter of the largest lesion = 3.0 cm) and lacked a central scar (1 of the 32 FNH in this group had a central scar). In the group with no history of malignancy, one of six patients had multiple lesions. Lesions in this group were larger (average diameter of the largest lesion = 5.3 cm) and were more likely to have a central scar (three of the six lesions had a central scar).

The multiplicity of lesions in long-term cancer survivors corresponds to other reports in the literature, although there are reports of cancer survivors with a solitary FNH [4, 5, 8–10, 12, 14, 15]. The clinical characteristics of patients in the literature with FNH and a history of malignancy are presented in Table 3. Multiple lesions in these patients support the hypothesis that the lesions are related to hepatotoxicity either from chemotherapy or radiation therapy as the effect is systemic.

The clinical characteristics of the two groups are also different. Patients with a remote history of malignancy were on average 7 years older at the time of diagnosis of FNH than patients with no prior malignancy. This age



Fig. 4 Axial T1-W image after administration of gadolinium in a 27-year-old man with a remote history of treated neuroblastoma shows multiple enhancing hepatic lesions (*arrows*). The lesions enhance homogeneously and there is no central scar

Table 3 Characteristics of FNH described in the literature in patients with a history of malignancy

Authors	Patient number	Gender	Age at diagnosis of FNH (years)	Time between diagnosis of malignancy and FNH (years)	Malignancy	Number of FNH lesions
Icher-De Bouyn CI, et al. [4]	1	F	18	4	Neuroblastoma	1
	2	M	11	8	Neuroblastoma	1
	3	M	13	11	Neuroblastoma	3
	4	F	20	7	Ewing sarcoma	2
	5	F	12	10	Medulloblastoma	1
	6	M	16	12	Neuroblastoma	1
	7	M	10	9	Neuroblastoma	1
	8	F	12	4	Neuroblastoma	1
	9	F	7	6	Neuroblastoma	1
	10	F	10	9	Neuroblastoma	1
	11	F	16	5	Ovarian germ cell tumor	1
	12	F	23	16	Ovarian germ cell tumor	4
	13	F	23	21	Sacrococcygeal germ cell tumor	6
	14	F	10	8	Neuroblastoma	1
Joyner BL Jr, et al. [5]	15	M	10	8	Neuroblastoma	3
	16	M	9	3	AML	1
	17	F	11	9	ALL	multiple
Junewick J, et al. [6]	18	Unk	Unknown	3	Neuroblastoma	multiple
Sorge I, et al. [7]	19	F	4	2	Adrenocortical carcinoma	13
Marabelle A, et al. [8]	20	M	13	12	Neuroblastoma	1
	21	M	27	27	Wilms tumor	1
	22	F	17	2	Monosomy 7, pancytopenia	1
Takeyama J, et al. [9]	23	M	6	5	Wilms tumor	1
Gutweiler JR, et al. [10]	24	M	4	2	Neuroblastoma	1
Friedl T, et al. [11]	25	F	22	8	Malignant gastrointestinal stromal tumor	4
	26	M	3	2	Neuroblastoma	6
	27	F	14	3	Wilms tumor	5
	28	M	4	2	Neuroblastoma	2
Anderson L, et al. [12]	29	F	20	17	ALL	2
	30	M	11	7	Hemophagocytic lymphohistiocytosis	1
	31	F	7	6	AML	multiple
Benz-Bohm G, et al. [13]	32	M	9	8	Neuroblastoma	2 ^a
	33	F	19	11	Neuroblastoma	2 ^a
	34	F	6	4	Neuroblastoma	3 ^a
	35	F	11	10	Neuroblastoma	3 ^a
	36	M	8	7	Neuroblastoma	3 ^a
	37	F	13	12	Neuroblastoma	4 ^a
Sudour H, et al. [14]	38	M	8	2	Aplastic anemia	3
	39	M	2	12	ALL	2
	40	F	19	5	AML	5
	41	F	18	13	AML	4
	42	M	8	7	ALL	5
	43	M	10	2	ALL	3
	44	F	12	6	Neuroblastoma	2
	45	M	21	3	AML	1
	46	M	8	5	AML	3
	47	F	13	4	AML	1
	48	F	22	10	Teratocarcinoma	3

Table 3 (continued)

Authors	Patient number	Gender	Age at diagnosis of FNH (years)	Time between diagnosis of malignancy and FNH (years)	Malignancy	Number of FNH lesions
	49	F	18	5	ALL	2
	50	M	17	9	ALL	1
	51	F	1	5	AML	3
	52	F	1	6	ALL	1
	53	F	13	3	AML	5
	54	F	9	6	Sickle cell disease	3
Kumagai H, et al. [15]	55	F	2	3	Wilms tumor	1

^a The number of lesions does not correspond to a specific patient

difference is of unknown significance. It is possible that patients without a history of cancer presented at a younger age because of the size of their lesions.

The female-to-male ratio was 1:3 in the cancer survivor group and 2:1 in the group with no history of malignancy. The ratio in cancer survivors differs from the general population where FNH is 2–8 times more common in females [2, 4]. It is possible that the frequency of males with FNH is increased in childhood cancer survivors because the associated malignancies, such as neuroblastoma, medulloblastoma and hepatoblastoma, are more common in males. Including our 7 patients, there are 62 reported patients with FNH after a remote history of childhood malignancy. The female-to-male ratio in this group is 34:27 (Table 3).

There are several limitations of this study including its small sample size and retrospective nature. Perhaps the largest limitation is that only pathologically proven cases of FNH were included in this study. As FNH is often a radiological diagnosis, the number of FNH lesions has been undercounted. This limitation particularly affects the group with no history of malignancy, as patients with a history of malignancy would likely be biopsied to exclude metastatic disease. The decision to include only patients with a pathologically proven FNH was made intentionally to ensure we were evaluating a homogeneous entity.

Conclusion

There appears to be two distinct groups of pediatric patients that are diagnosed with FNH: long-term cancer survivors and patients with a sporadic liver lesion. Long-term cancer survivors typically have multiple hepatic lesions, small masses and no central scar. In this study, these patients were more likely to be male and had small masses that presented

later in life. As pediatric radiologists and oncologists begin to counsel patients and their families prior to biopsy, it is important for them to be aware that multiple enhancing hepatic lesions in cancer survivors might represent FNH rather than metastatic disease.

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