Focal nodular hyperplasia of the liver: results of treatment and options in management

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Abstract
Twenty two patients (19 females) with focal nodular hyperplasia were seen between 1973 and 1989. Five were children, and all the adults were aged under 42 years (median 33 years). Fourteen patients (64%) were symptomatic on presentation. Twelve of the 14 adult women had taken the oral contraceptive pill. Twelve patients, nine of whom were symptomatic, underwent hepatic resection shortly after presentation. There were no deaths or major complications, and all remain well on follow up. Four patients underwent either hepatic artery embolisation or ligation. After an interval of six to 10 years they were asymptomatic and only one has histological evidence of residual focal nodular hyperplasia. Of five patients initially treated conservatively, two were asymptomatic and have remained so for three and 13 years. One of the three symptomatic patients became symptom free after stopping the contraceptive pill. The management of focal nodular hyperplasia requires a flexible approach. Lesions which are asymptomatic can be observed with regular ultrasound and treated if they enlarge or become symptomatic. Symptomatic patients who present while taking the contraceptive pill can also have a trial of conservative treatment. Other symptomatic patients, including those who previously took the pill, are best treated by surgical resection, and, where this is not possible, by embolisation.

Focal nodular hyperplasia of the liver is a rare benign lesion that occurs predominantly in women during their reproductive years. Previously it was referred to by a variety of names until Edmondson' introduced the term 'focal nodular hyperplasia' in 1958. It consists of a well circumscribed region of hyperplastic liver parenchyma often containing a stellate fibrous scar. Most reported cases have presented as incidental findings, and the aetiology and natural history of this condition remain largely unknown. Consequently, the correct choice of management is unclear. In this study we have reviewed our experience of 22 patients with this condition as the basis of formulating a plan of management.

Patients and methods
Between 1973 and 1989, 22 patients (19 females and three males) with focal nodular hyperplasia were seen at King's College Hospital. Details of the patients are given in the Table. There were five children. All adults were aged under 42 years (median 33 years). Fourteen patients (64%) presented with either pain or a mass. In the remaining eight patients focal nodular hyperplasia was an incidental finding at laparotomy (three), on an abdominal examination (two), on an abdominal ultrasound (one), in a resected liver specimen separate from fibrolamellar carcinoma (one), and as an incidental finding at necropsy in a 13 year old girl with von Gierke's disease (type I glycogen storage disease) who had died during a portocaval shunt procedure. Focal nodular hyperplasia was situated in the right hepatic lobe in 16 patients, in the left lobe in three patients, across the interlobar plane in two patients, and in both lobes in one patient. Histological confirmation of focal nodular hyperplasia was obtained in all patients. Eight patients did not undergo resection of focal nodular hyperplasia and in these the diagnosis was made by open biopsy in five and by Trucut needle biopsy in three.

Results
Twelve of the 14 adult females had at some time taken the oral contraceptive pill. None took it after the diagnoses of focal nodular hyperplasia were made. Twelve of the 22 patients, nine of whom were symptomatic with pain or a mass, underwent hepatic resection shortly after presentation. One further symptomatic patient (case 13) was initially treated conservatively but the symptoms continued and he underwent resection three years after diagnosis. There were no deaths or major postoperative complications. All patients were reviewed between six months and nine years after operation and all were asymptomatic with no clinical or radiological evidence of focal nodular hyperplasia.

Four patients have been treated conservatively. Two of these were asymptomatic and have remained so for three and 13 years respectively. One patient (case 20) presented with abdominal pain related to focal nodular hyperplasia. She stopped taking the contraceptive pill and is now asymptomatic. The final patient (case 21) presented with a large hepatic mass associated with pain. At laparotomy a wedge biopsy specimen showed focal nodular hyperplasia, but it
Details of Patients

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age/sex</th>
<th>OCP</th>
<th>Symptoms</th>
<th>Liver segment(s)</th>
<th>Size (cm)</th>
<th>Treatment</th>
<th>Follow up</th>
<th>Comments</th>
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<tbody>
<tr>
<td>1</td>
<td>5F</td>
<td>–</td>
<td>Incidental (laparotomy)</td>
<td>2-4</td>
<td>11</td>
<td>Resection</td>
<td>2 mths well</td>
<td></td>
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<tr>
<td>2</td>
<td>6F</td>
<td>–</td>
<td>Pain</td>
<td>5,6</td>
<td>9</td>
<td>Resection</td>
<td>3 yr well</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6F</td>
<td>–</td>
<td>Pain; mass</td>
<td>2,3</td>
<td>9</td>
<td>Resection</td>
<td>2 yr well</td>
<td></td>
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<td>13F</td>
<td>–</td>
<td>Pain</td>
<td>8</td>
<td>8</td>
<td>Resection</td>
<td>3 mths well</td>
<td></td>
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<td>7</td>
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<td>9 mths well</td>
<td></td>
</tr>
<tr>
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<td>27F</td>
<td>Yes</td>
<td>Incidental</td>
<td>5</td>
<td>5</td>
<td>Resection</td>
<td>9 mths well</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>28F</td>
<td>Yes</td>
<td>Pain</td>
<td>2-4</td>
<td>11</td>
<td>Resection</td>
<td>1 yr well</td>
<td>Pain for 3 yr after diagnosis before undergoing resection</td>
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<tr>
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<td>Yes</td>
<td>Pain; mass</td>
<td>4</td>
<td>8</td>
<td>Resection</td>
<td>15 mths well</td>
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<td>3</td>
<td>8</td>
<td>Resection</td>
<td>18 mths well</td>
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<td>4</td>
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<td></td>
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<tr>
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<td>Yes</td>
<td>Pain</td>
<td>5</td>
<td>5</td>
<td>Resection</td>
<td>6 yr well</td>
<td></td>
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<tr>
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<td>Yes</td>
<td>Incidental (mass)</td>
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<td>8</td>
<td>Resection</td>
<td>9 yr well</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>45M</td>
<td>–</td>
<td>–</td>
<td>2,3</td>
<td>6</td>
<td>Resection</td>
<td>5 cm area of focal nodular hyperplasia remains</td>
<td>Biopsy 5 yr later - no focal nodular hyperplasia</td>
</tr>
<tr>
<td>14</td>
<td>3M</td>
<td>–</td>
<td>Incidental (mass)</td>
<td>4,5,8</td>
<td>6</td>
<td>Ligation of right hepatic artery + embolisation</td>
<td>16 yr well</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>30M</td>
<td>–</td>
<td>Mass</td>
<td>7,8</td>
<td>14</td>
<td>Embolisation</td>
<td>9 yr well</td>
<td>Ultrasound now normal</td>
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<td>7</td>
<td>7</td>
<td>Embolisation</td>
<td>3 yr well</td>
<td>Ultrasound shows 6 cm abnormal area</td>
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<td>37F</td>
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<td>5-8</td>
<td>14</td>
<td>Embolisation</td>
<td>6 yr well</td>
<td></td>
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<tr>
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<td>No</td>
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<td>5</td>
<td>Conservative</td>
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<td></td>
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<tr>
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<td>No</td>
<td>Incidental (ultrasound)</td>
<td>8</td>
<td>4</td>
<td>Conservative</td>
<td>3 yr well</td>
<td></td>
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<tr>
<td>20</td>
<td>41F</td>
<td>Yes</td>
<td>Pain</td>
<td>6</td>
<td>6</td>
<td>Conservative</td>
<td>2 yr well</td>
<td>Symptoms disappeared after stopping OCP</td>
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<tr>
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<td>Yes</td>
<td>Pain</td>
<td>1,3,5-8</td>
<td>22</td>
<td>Conservative</td>
<td>1 yr –</td>
<td>Remains symptomatic; will undergo embolisation von Gierke’s disease; multiple areas of focal nodular hyperplasia</td>
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<tr>
<td>22</td>
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<td>Incidental (necropsy)</td>
<td>1-9</td>
<td>&lt;13</td>
<td>–</td>
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</table>

OCP=oral contraceptive pill.

Focal nodular hyperplasia was considered to be unresectable. She remains asymptomatic nine months later and is being considered for tumour embolisation.

Four patients, two of whom were asymptomatic, have undergone embolisation of their focal nodular hyperplasia. A three year old boy (case 14), previously described, presented with focal nodular hyperplasia as an incidental finding. At laparotomy the lesion was unresectable and hepatic artery ligation was performed. A liver biopsy specimen six months later showed fibrosis but no evidence of focal nodular hyperplasia. Ten years later a mass measuring 6 cm on ultrasonography was palpable in the right upper quadrant of the abdomen and biopsy specimens showed focal nodular hyperplasia. For the past four years he has remained asymptomatic and the size of the lesion is unchanged. A 30 year old man (case 15) presented with a mass in the right hypochondrium. It measured 14 cm and because of its position in the liver was considered to be unresectable. He underwent hepatic artery embolisation and subsequent right hepatic artery ligation. Eight months later when the tumour had reduced to 5 cm in size a further arterial embolisation was performed. A biopsy specimen five years later showed no evidence of focal nodular hyperplasia, and he remains symptom free. A 37 year old woman (case 17) presented with pain and a 14 cm area of focal nodular hyperplasia in the right lobe of the liver. Embolisation was performed and over the past six years the tumour has reduced in size to 6 cm. She remains asymptomatic. A 33 year old woman (case 16) was found to have a 7 cm area of focal nodular hyperplasia during an elective cholecystectomy. Subsequent arteriography showed the lesion to be very vascular and it was treated with right hepatic artery embolisation. Four years later the patient remains asymptomatic and ultrasound shows only a small residual abnormal area within the liver.

Discussion

Focal nodular hyperplasia is a benign liver lesion composed mainly of hepatocytes and Kupffer cells. Typically it has a central stellate scar with radiating septae and is surrounded by a thin capsule. Within the septa and vessels channels and foci of proliferating bile ducts are present. Lesions may be multiple. Focal nodular hyperplasia, hepatic adenoma, and fibrolamellar carcinoma are usually distinct entities, but some lesions may be difficult to differentiate. Areas of focal nodular hyperplasia have been found in a tumour mass of adenoma or fibrolamellar carcinoma.

It is more common in women. Although there is a strong association between the oral contraceptive pill and hepatic adenomas, the association of focal nodular hyperplasia with the contraceptive pill is reported to be less common, being present in 50-75% of women. In our series all but two women had at some time taken an oral contraceptive. Both focal nodular hyperplasia and hepatic adenomas may occur together in women taking oral contraceptives, and in one report both lesions were present in a male with high concentrations of endogenous sex steroids. When focal nodular hyperplasia is associated with oral contraceptives the lesions tend to be larger, symptoms more common and, if there is prolonged use, haemangiomas frequently coexist.

The aetiology is unknown. Many believe it is a hyperplastic response of the hepatic parenchyma to a pre-existing arterial malformation since many of these tumours have a pronounced vascular supply. Focal nodular hyperplasia shows a
much greater degree of vascular intimal and medial alterations than hepatic cell adenoma, and these alterations are especially manifest in users of the oral contraceptive pill. Consequently, it has been suggested that focal nodular hyperplasia develops in these patients as a result of the effect of oral contraceptives on the hepatic vasculature. This series differs from other large series in that most patients were symptomatic from the focal nodular hyperplasia at presentation. In a 20 year review from the Mayo Clinic only four of 41 adult patients were symptomatic. The others presented as incidental laparotomy findings (22) or necropsy findings (11) or were discovered at routine physical examination (four). In three large collected series only 53 (23%) of 229 patients with focal nodular hyperplasia were symptomatic at the time of diagnosis.

One of the reasons why so many of our patients were symptomatic at presentation may relate to the size of the lesions. Sixty five per cent of adult patients had lesions 7 cm or greater compared to less than 16% in other series. Lesions tend to be larger in children in whom there are often associated congenital abnormalities. One child in our study had type I glycogen storage disease (von Gierke's disease) and was found at necropsy to have multiple nodules of focal nodular hyperplasia in the liver, an association previously reported by Goldstein et al and Pizzo.

Radiology, with the use of multiple imaging techniques, has been reported to make an accurate diagnosis in 75% of patients. In our unit a combination of clinical, biochemical, and radiological investigations provides an accurate preoperative diagnosis for all solid hepatic lesions in 95% of patients and for focal nodular hyperplasia in 83% of patients. Focal nodular hyperplasia may show a central scar on computed tomography, ultrasonography, or angiography, and in the last investigation a typical hypervascular spoke wheel configuration of feeding vessels producing a dense capillary blush is uncommon but characteristic. Increased density of lesions on isotopic scans is diagnostic, but normal or reduced density compared to surrounding hepatic parenchyma may occur. Most patients have normal liver function tests. In young women the main differential radiological and clinical diagnosis is hepatic adenoma and in other groups conditions that may also require surgical treatment. Therefore it is important to obtain histological confirmation of focal nodular hyperplasia if conservative treatment is to be considered. We recommend needle liver biopsy (Trucut) under either ultrasound or computed tomographic control. Interpretation of the biopsy specimen may be difficult and we recommend that the sections be reviewed by a histopathologist with a specific interest in hepatic disorders. If the lesion is to be resected, whether the actual histology is focal nodular hyperplasia or not, we would not recommend biopsy since needle tract recurrence may follow biopsy of a malignant lesion.

The management remains controversial, since the natural history of this condition has not been fully elucidated. It is recommended that asymptomatic hepatic adenomas be treated since they may be complicated by haemorrhage or malignant transformation. Haemorrhage from focal nodular hyperplasia is a rare complication, occurring predominantly in lesions associated with the contraceptive pill. Some reports in which focal nodular hyperplasia is reported to have bled have had either incomplete reports of the histology or descriptions suggestive of hepatic adenoma. There is no evidence that focal nodular hyperplasia can undergo malignant transformation, but areas of focal nodular hyperplasia may be seen on the periphery of the fibrolamellar variant of hepatocellular carcinoma. A resected liver specimen from one of our patients showed an area of focal nodular hyperplasia separate from a fibrolamellar carcinoma.

There is little published information on the progress of patients with asymptomatic focal nodular hyperplasia. In the Mayo Clinic series follow up was available for 10 of the 13 asymptomatic patients in whom the lesion was biopsied and left in situ. These patients remained asymptomatic during a mean 18–175 months of follow up, but it is not stated whether there had been any change in the size of the tumours during this period. Only two of our patients were asymptomatic and treated conservatively. Both have remained asymptomatic three and 13 years after diagnosis. We recommend that patients with asymptomatic focal nodular hyperplasia should be treated conservatively, avoid the contraceptive pill, and have regular follow up. If the patient becomes symptomatic or the lesion enlarges then resection should be considered. Regression of focal nodular hyperplasia can occur after withdrawal of the oral contraceptive pill, but pregnancy may be associated with tumour enlargement.

The correct treatment for the patient with symptomatic focal nodular hyperplasia is also debatable. All three of the Mayo Clinic patients who had abdominal pain related to the tumour remained symptomatic. Only three of our patients who were initially treated conservatively were symptomatic at presentation. One man (case 13) continued to have symptoms for three years before undergoing resection. During this time the tumour remained unchanged in size. The second patient, a 41 year old woman (case 21), who had taken the contraceptive pill in the past was found to have an unexcitable 22 cm tumour at laparotomy, and she remains symptomatic. The third patient, another 41 year old woman (case 20), who was taking the oral contraceptive pill at presentation, has become asymptomatic two years after diagnosis. The remainder of the symptomatic patients have been treated with surgical excision of the tumour. Liver resection is now associated with a low mortality, and no deaths have resulted from hepatic resection in this or other large series. All of our patients who underwent resection were symptom free at follow up.

As it has been suggested that focal nodular hyperplasia is a hyperplastic response of the hepatic parenchyma to a pre-existing arterial malformation embolisation or hepatic ligation may seem a logical option in the management. We have treated four patients in this way (one of whom has been reported previously), but have
been able to find only one other published case treated similarly. Apart from a pronounced but temporary fever, the procedures have been uncomplicated. All four patients have had a reduction in the size of the lesion and, when present, symptom relief. One has been shown subsequently to have histologic evidence of focal nodular hyperplasia, and two others still have abnormal scans. Hepatic resection is the preferred treatment for most symptomatic lesions, but when contraindicated or surgically not possible embolisation may be a suitable alternative. For small lesions superselective embolisation can be performed and this will minimise the degree of hepatic ischaemia to the remainder of the hepatic lobe.

The management of focal nodular hyperplasia requires a flexible approach. Asymptomatic lesions can be observed safely with regular ultrasound, and treated if they become symptomatic or enlarge. Patients presenting with symptomatic lesions while taking the contraceptive pill can also have a course of conservative treatment. Other symptomatic patients, including those with a previous history of taking the contraceptive pill, are best treated by surgical resection, and, where not possible, by embolisation.