

# Incidence of hepatic hamartomas in tuberous sclerosis

S Józwiak, M Pędich, P Rajszyś, R Michalowicz

## Abstract

Hepatic hamartomas were thought to be a rare finding in patients with tuberous sclerosis. The purpose of this study was to assess their incidence in children with tuberous sclerosis and to review the literature.

During 1984-90 we examined 51 children by ultrasonography; there were 25 boys and 26 girls. Their age ranged from 3 months to 18 years. Liver hamartomas were seen in 12 (23.5%) of the children, more often in girls than boys (5:1). Their incidence increased with age reaching 45% in children over the age of 10. They did not produce any symptoms of hepatic dysfunction.

Our study and review of reported cases prove that hepatic hamartomas are a common finding in patients with tuberous sclerosis and may be very helpful in providing a more accurate diagnosis and consequently help in genetic counselling.

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Child's Health Centre,  
Warsaw,  
Poland,  
Department of  
Child Neurology  
S Józwiak  
R Michalowicz

Department of Radiology  
M Pędich  
P Rajszyś

Correspondence to:  
Dr Sergiusz Józwiak,  
Department of  
Child Neurology,  
Child's Health Centre,  
Al Dzieci Polskich 20,  
04-736 Warszawa,  
Poland.

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Tuberous sclerosis is a genetic disorder with multiple hamartomas, autosomal dominant inheritance, variable expressivity, and high penetrance. Its expression may vary greatly with some individuals showing no clinical signs of the disorder and others manifesting severe seizure disorders, mental retardation, and involvement of multiorgan systems including skin, brain, heart, kidneys, retina, and liver.

The most common visceral lesions are renal angiomyolipomas, which have been studied extensively by others and are found in 52-89% of patients.<sup>1 2</sup>

Hamartomas of the liver in association with tuberous sclerosis are usually found incidentally

on postmortem examination,<sup>3 4</sup> with selective angiography,<sup>5-7</sup> computed tomography,<sup>8 9</sup> or by ultrasonography.<sup>10-12</sup> The incidence of hepatic lesions, however, has been evaluated in only one large study.<sup>12</sup>

We evaluated the incidence of hepatic hamartomas in children with tuberous sclerosis and reviewed the literature on previously reported cases.

## Patients and methods

During the period 1984-90 we examined 51 children by ultrasonography; there were 25 boys and 26 girls. The age of patients ranged from 3 months to 18 years (mean age 6.8 years). There were 20 patients under 5 years of age, 20 children between 5 and 10 years, and 11 patients over the age of 10.

The diagnosis of tuberous sclerosis was established in all patients by careful history taking and examination of the skin, nails, hair, and eyes according to the Gomez criteria for tuberous sclerosis.<sup>13</sup> Cerebral computed tomography and ultrasonography of the heart were also done.

Ultrasonographic examinations of the upper abdomen were performed with a sector scanner, using a 3.75 or 5 MHz transducer to evaluate the liver, kidneys, pancreas, and spleen. Four parents with tuberous sclerosis were examined by the same method.

## Results

Hepatic hamartomas were seen in 12 (23.5%) of the 51 examined children. They were found more often in girls than boys (5:1) and their incidence increased with age.

Areas of increased echogenicity compared with the surrounding hepatic parenchyma were found in two out of the 20 children (10%) below the age of 5 years (an 8 month old girl and a 1.5 year old boy), in five out of the 20 children (25%) between 5 and 10 years, and in five out of the 11 patients (45%) over the age of 10. Usually, the hamartomas were multiple (n=9) and localised in both liver lobes. They all measured from 0.5 to 0.8 cm in size. Calcification in these lesions was found in two girls aged 10 and 12 years (table 1).

In nine out of 12 children with liver involvement ultrasonography also revealed multiple bilateral angiomyolipomas of the kidneys. In two of these children renal angiomyolipomas coexisted with cysts and in one 9 year old girl, renal angiomyolipomas coexisted with a clear cell sarcoma. After several years of good health,

Table 1 Ultrasonographic findings in 12 children and three parents with liver hamartomas associated with tuberous sclerosis

Case No	Age (years)	Sex	Liver lesion	Associated kidney lesion
1	12	F	Multiple, largest 0.7 cm	AML
2	12	F	Multiple, 0.5-0.7 cm, calcification, right lobe	AML
3	10	F	Single, calcification, right lobe	AML, cysts
4	1.5	M	Single, 0.6 cm, left lobe	None
5	8	F	Multiple, 0.5-0.7 cm	None
6	13	F	Multiple, largest 0.7 cm	AML
7	5	F	Multiple, 0.5 cm	None
8	9	F	Multiple, 0.5-0.8 cm	AML, clear cell sarcoma
9	0.7	F	Multiple, 0.5 cm	AML
10	6	M	Single, 0.7 cm, right lobe	AML
11	8	F	Multiple, 0.5-0.7 cm	AML, cysts
12	13	F	Multiple, largest 0.8 cm	AML
13	35	F	Multiple, largest 2.5 cm	AML
14	22	F	Single, 0.7 cm, right lobe	AML
15	41	M	Multiple, 0.5-0.8 cm	None

AML=angiomyolipoma.

during which this girl did not come for follow up examination, she developed a relapsing fever. Except for the hepatic hamartoma, ultrasound study of the kidneys showed a large tumour of 6×6×9 cm in the right kidney and bilateral, multiple angiomyolipomas. She underwent radical nephrectomy but died three months after surgical intervention.

In none of the children, with the exception of the girl with renal clear cell sarcoma, did we observe any clinical symptoms or signs of hepatic or renal dysfunction. The blood pressure and all biochemical tests including concentrations of electrolytes, serum creatinine, and uric acid and activities of alkaline phosphatase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase were within normal limits. There was no blood or protein in the urine.

Hepatic hamartomas were seen in three out of four parents with tuberous sclerosis: two women and one man. Both women, 22 and 35 years of age, demonstrated hepatic hamartomas coexisting with multiple renal angiomyolipomas. Similar changes, both hepatic and renal, were revealed in their daughters, 8 months and 12 years of age, respectively. Ultrasonographic examination of the 41 year old man showed multiple hepatic hamartomas and a normal picture of both kidneys.

### Discussion

For many years hepatic hamartomas were regarded as an unusual finding in tuberous sclerosis. However, we have found 28 patients with tuberous sclerosis and liver involvement in the medical literature (table 2).

The incidence of hepatic lesions has been evaluated only in two reports.<sup>6,12</sup> Compton *et al* demonstrated vascular tumours of the liver with coeliac angiography in five out of eight patients; their ages were 10 months (two patients), 11·2 and 29 years.<sup>6</sup> In the study of Fleury *et al* hepatic hamartomas were revealed by ultrasonography in 13% of patients (three out of 23) under 16 years of age and in 23% (three out of 13) in the older patients.<sup>12</sup>

Our results prove that the incidence of

hepatic hamartomas may be even higher, reaching 45% in children above 10 years of age.

In the reviewed literature hepatic hamartomas were found more often in females than males, with the ratio 19:9. In our study this predominance was even more apparent (5:1).

Hepatic hamartomas in tuberous sclerosis seem to be benign and asymptomatic. In contrast to renal lesions, hepatic hamartomas were not mentioned as a possible cause of death in patients with tuberous sclerosis in a large study of 355 patients at the Mayo Clinic.<sup>21</sup>

None of the children examined in our study had any manifestation of hepatic dysfunction. In the literature we could not find any description of hepatic manifestations in tuberous sclerosis patients with liver involvement except for one patient presented by Kristel and Sperber.<sup>20</sup> These authors described a 10 year old girl with tuberous sclerosis who was examined after blunt abdominal trauma. Computed tomography and ultrasound showed a hepatic tumour in the left lobe, which enlarged during the next several months and forced them to carry out a hepatic lobectomy.

Histopathological examination of hepatic hamartoma was available in several cases. Hepatic angiomyolipomas were the most common tumours found in patients with tuberous sclerosis.<sup>10,16,18,20</sup> The other reports also mentioned neurilemmoblastoma,<sup>14</sup> lipomesenchymal tumour,<sup>15</sup> hamartoma,<sup>3</sup> and lipoma.<sup>17</sup>

Interestingly, haemangioma, the most common benign tumour of the liver was not seen in any of histopathologically examined patients with tuberous sclerosis.

Diagnosis of vascular hepatic tumours in tuberous sclerosis was suggested in several reports in angiographic<sup>6-8</sup> and ultrasonographic studies.<sup>12</sup> We suppose that angiographic findings in the liver of patients with tuberous sclerosis may resemble vascular expression of angiomyolipomas more than real haemangioma. Unfortunately, computed tomography of the liver was not performed in any of the aforementioned studies.

The ultrasonographic appearance of lipomatous masses cannot be easily differentiated from haemangioma. The pattern is not specific for angiomyolipomas, therefore, ultrasound studies should be supplemented by computed tomography. Contrast enhanced computed tomography is able to provide greater detail by demonstrating low density areas that represent fatty tissue.

We believe that the diagnosis of hepatic angiomyolipomas in our patients is highly probable. But as none of them presented symptoms of hepatic dysfunction, and, as patients with liver hamartomas in tuberous sclerosis seem to have a good prognosis, we decided not to perform computed tomography as a routine procedure. Ultrasonographic assessment of the liver should be performed together with kidney evaluation in follow up studies.

Roberts *et al* stressed a relationship between renal angiomyolipomas and hepatic tumours in patients with tuberous sclerosis.<sup>19</sup> Their study of a group of 50 patients with renal angiomyo-

Table 2 Hepatic hamartoma: review of the literature (total 28: 19F/9M)

Authors (in chronological order)	No of patients	Sex	Age (years)	Diagnosis of liver lesions
Inglis <sup>14</sup>	1	F	41	Neurilemmoblastomas
Cares <sup>15</sup>	1	F	25	Lipomesenchymal tumours
Perou and Gray <sup>16</sup>	1	F	28	AML, polycystic lesions
Viamonte <i>et al</i> <sup>3</sup>	1	F	25	Hamartoma
Ramchand <i>et al</i> <sup>17</sup>	1	M	24	Lipoma
Chonko <i>et al</i> <sup>5</sup>	1	F	22	Vascular abnormalities
Compton <i>et al</i> <sup>6</sup>	5	F	11	Hamartoma
		F	10/12	Hamartoma
		M	29	Hamartoma
		F	24	Hamartoma
		F	10/12	Hamartoma
Kagan and Steckel <sup>10</sup>	1	M	11	AML
Grasso <i>et al</i> <sup>4</sup>	1	M	1/12	Atypical, large hepatocytes
Newmark <i>et al</i> <sup>8</sup>	1	F	52	AML
Marsidi and Wise <sup>7</sup>	1	F	23	Precapillary angiomas
Ilgren and Westmoreland <sup>18</sup>	1	F	21	AML
Rosen <i>et al</i> <sup>9</sup>	1	M	28	Fatty lesion, AML?
Roberts <i>et al</i> <sup>19</sup>	3	M	26	Lipomatous tumors, AML?
		F	23	Lipomatous tumors, AML?
		F	42	Lipomatous tumors, AML?
Fleury <i>et al</i> <sup>12</sup>	6	2M/4F	6-48	Harmartomas. Haemangiomas?
Kristal and Sperber <sup>20</sup>	1	F	10	AML
Green <i>et al</i> <sup>11</sup>	1	M	40	Fibromas

AML-angiomyolipoma.

lipomas revealed lipomatous tumours of the liver in five patients. Three of them were known to be affected with tuberous sclerosis.

Renal angiomyolipomas were found in 85% (24/28) of tuberous sclerosis patients with liver involvement reported in the literature and in 75% (9/12) of children in the presented study. However, these figures cannot prove that any relationship between renal and hepatic angiomyolipomas exists. In our experience renal angiomyolipomas appear before hepatic hamartomas and both develop with age. This evolution of the lesions may result in their frequent coexistence in older children and adults.

We conclude that liver hamartomas are a very valuable feature in the diagnosis of tuberous sclerosis, especially of formes frustes. In the absence of long term studies, periodic monitoring with hepatic and renal ultrasonography is recommended for all patients with tuberous sclerosis.

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