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Renal angiomyolipomata and learning difficulty in tuberous sclerosis complex

EDITOR—Tuberous sclerosis complex (TSC) is a dominantly inherited disease of high penetrance, characterised pathologically by the presence of hamartomata in multiple organ systems. Well known clinical manifestations include epilepsy, learning difficulties, behavioural problems, and skin lesions. Many patients have renal lesions, usually angiomyolipomata (AML), which can cause clinical problems secondary to haemorrhage or by compression and replacement of healthy renal tissue, which rarely causes end stage renal failure.[1] Cysts, polycystic renal disease, and renal carcinoma can also occur. Polycystic disease has an early onset clinically and is the result of large contiguous deletions on chromosome 16 affecting both the *TSC2* gene and the gene for adult onset polycystic kidney disease.[2] Tuberous sclerosis complex exhibits genetic heterogeneity.[3] Mutations in two recently identified genes, *TSC1* at 9q34 and *TSC2* at 16p13, each result in an apparently similar phenotype, although recent work has suggested that mutations in *TSC2* may be associated with more severe disease.[4] Both genes are tumour suppressor genes, the strongest evidence for this being the loss of heterozygosity around the normal gene at 9q34 or 16p13 in hamartomata from tuberous sclerosis patients.[5 6] There is evidence that the severity of learning difficulties in tuberous sclerosis complex is related to the number of hamartomata in the brain.[7] Until now, no one has reported on a correlation between the severity of the phenotype in two or more organs. We report on a correlation between renal hamartomata and learning difficulties in a population based sample of tuberous sclerosis complex patients (table 1).

As part of a larger prevalence study that began in 1985, patients identified with tuberous sclerosis complex and living in the Bath Health District have been followed longitudinally. All patients have undergone at least one abdominal ultrasound examination, performed by the authors, during the last two years. We investigated the association between angiomyolipomata and intellectual impairment because of an apparent association we had noticed in our clinical work with TSC patients (table 1). We made no attempt to explore any other associations. The presence of learning difficulty in this population was ascertained as previously described.[8] The correlation between renal angiomyolipomata and learning difficulty was analysed using a two sided Fisher's exact test (table 2). Of 22 patients known to be alive and living in the Bath Health District in August 1998, nine had learning difficulties and all had angiomyolipomata. Thirteen patients were of normal intellect and five of these had angiomyolipomata (p=0.006).

This apparent association between renal angiomyolipomata in tuberous sclerosis complex and learning difficulties has not previously been noted. The association reaches statistical significance despite the small numbers

Table 1 Angiomyolipomata and learning difficulties in TSC patients

AML + / LD +	*AML + / LD −*	*AML − / LD −*	*AML − / LD +*
M 24 y	F 19 y	M 86 y	
M 29 y	F 62 y	M 45 y	
M 42 y	F 13 y	F 22 y	
F 38 y	F 16 y	F 59 y	
M 10 y	M 26 y	F 33 y	
M 11 y		M 6 y	
M 6 y		M 24 y	
M 9 y		F 46 y	
F 10 y			

AML = angiomyolipoma.
LD = learning difficulty.
M = male.
F = female.
y = years.

Table 2 Two sided Fisher's exact test

	Learning difficulties	
	+	−
Renal angiomyolipomata		
+	9	5
−	0	8

p=0.006

involved in the study and remains significant even when two patients of normal intellect and isolated renal cysts are transferred from the unaffected to affected groups (p=0.046); it is possible that renal cysts may form in TSC because renal tubules are blocked by small renal angiomyolipomata. We do not think there is an absolute correlation between learning difficulty and renal angiomyolipomata; we have patients outside the Bath district with learning difficulties and no renal pathology.

The age range in our population is 6-86 years (median 24 years). Using Wilcoxon rank sum tests we found no significant association between age and learning difficulty (p=0.09) or between age and the presence of AMLs (p=0.09) in this population. Similarly there is no evidence of a significant relationship between gender and either learning difficulty (p=0.1) or AML presence (p=1.0) when the relationships are independently investigated using Fisher's exact tests. There is no reason to suppose, therefore, that the association described between intellectual impairment and renal angiomyolipomata is confounded significantly by either gender or age in this sample.

One explanation for the observed correlation would be that certain patients with tuberous sclerosis complex have an increased propensity to the formation of hamartomata resulting both in more cerebral tubers (and therefore a higher risk of learning difficulties) and in a greater likelihood of renal angiomyolipoma formation. Previously, patients with tuberous sclerosis complex and learning difficulty appear to have had a reduced life expectancy; epidemiological surveys have consistently shown lower than expected numbers of elderly tuberous sclerosis patients with learning difficulties.[8] We believe this is because of an increased death rate among this group from epilepsy, brain tumours, and intercurrent illness. However, with changing attitudes to the management of patients with learning difficulties, improved management of epilepsy, and more vigilant surveillance, more of these patients survive into adulthood. One implication of our finding is that we will see an increase in complications from renal hamartomata as more tuberous sclerosis patients with intellectual difficulties survive for longer.

FINBAR J K O'CALLAGHAN*
MICHAEL NOAKES†
JOHN P OSBORNE*

**Bath Unit for Research in Paediatrics, Children's Centre, Royal United Hospital, Combe Park, Bath BA1 3NG, UK*

†Department of Radiology, Royal United Hospital, Combe Park, Bath BA1 3NG, UK

Correspondence to: Professor Osborne

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Clinical geneticists' attitudes and practice towards testing for breast cancer susceptibility genes

EDITOR—Cancer genetics, and in particular breast cancer genetics, is the fastest expanding discipline within clinical genetics. Cancer referrals now constitute a third of all referrals to most clinical genetics centres. Currently there are no national guidelines on predictive testing for *BRCA1* and *BRCA2*. Several members of the same family may be seen in different centres and offered different clinical management. Such differences may in part be attributable to differences in funding of genetic services and testing at the service or research level, but it is clear that this area also involves various ethical dilemmas that may well be viewed differently by different practitioners. In order to investigate the nature and degree of variation that exists in practice and attitudes among clinical geneticists, we have undertaken a survey of all clinical geneticists in the United Kingdom who deal with cancer genetics.

Four clinical case scenarios were devised from the authors' own clinical experience to assess attitudes and practice towards breast cancer gene testing. Questionnaires were sent to 57 geneticists in the United Kingdom, representing all specialist registrar and consultants involved in cancer genetics. Each was asked to respond to questions relating to each scenario and to state the reasons for their decisions. Forty seven completed questionnaires were received (83% compliance). All clinical genetics centres in the UK were represented by at least one response. In three instances a joint response involving more than one geneticist from a centre was returned. The four clinical cases are given below. For each case the salient points raised by selected respondents for arriving at their decision are given.

Case 1. A woman has been shown to carry a pathogenic mutation in the *BRCA1* gene. She is 9 weeks pregnant and requests a prenatal test to see whether the fetus also carries this mutation. Participants were asked whether they would be prepared to offer prenatal testing after appropriate counselling.

Twenty four (51%) respondents stated that they would be prepared to offer prenatal testing to the woman after counselling. Fifteen (32%) said they would not and 17% did not know what their action would be. Most of the respondents who would offer such testing indicated that if the counsellors had given all the relevant information, it was up to the woman to make a decision. Most commented that the woman's experience of cancer in the family was likely to be a strong motivating factor in the decision to request prenatal diagnosis and that counsellors were not in a position to deny this experience. Many also commented that a pregnancy could be terminated anyway for "social"