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Causes of mortality in individuals with Tuberous Sclerosis Complex

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Causes of mortality in TSC

ABSTRACT

Aim
The causes of death in patients with tuberous sclerosis complex (TSC) have rarely been studied, with only one published account, which was reported from the Mayo Clinic in 1991. We aimed to investigate mortality in a large cohort of TSC patients from one of two national referral clinics in the UK.

Method
We identified 284 patients who attended Bath TSC clinic between 1981 and 2015 and ascertained causes of death by reviewing medical records, death certificates and post-mortem reports.

Results
Sixteen patients died from complications of TSC: eight from TSC kidney diseases; four from Sudden Unexpected Death in Epilepsy (SUDEP); two from lymphangioleiomyomatosis; one from a subependymal giant cell astrocytoma; and one from a pancreatic malignancy. The median age of death was 33 years (IQR 26-46). Mortality was significantly more common in patients with learning-disability than in those without (13/135 (9%) vs 3/131 (2%), $P = 0.02$) (two-tailed Fisher exact test).

Interpretation
Renal disease is a major cause of mortality in TSC. Lifelong surveillance and early intervention is warranted. SUDEP is also an important cause of mortality. Patients with learning disabilities are at significantly greater risk of early mortality and this implies the need for greater vigilance for TSC related complications in this group. Female patients are vulnerable to pulmonary and renal disease. Pancreatic lesions are a rare but potentially treatable cause of mortality.

What this paper adds

1. SUDEP is an important cause of mortality in TSC patients.
2. Patients with learning disabilities are at significantly greater risk of early mortality.
3. Female patients are more vulnerable to renal and pulmonary disease compared with male patients.
4. Less well-known manifestations of TSC, such as pancreatic malignancy, are important causes of death.

Tuberous Sclerosis Complex (TSC) is a genetic condition caused by mutations in the tumour suppressor genes TSC1 and TSC2, located on chromosomes 9 and 16 respectively.[1, 2] Approximately two-thirds of cases occur sporadically and the overall incidence has been estimated to be 1 per 5,800 live births.[3]

The protein products of TSC1 and TSC2, hamartin and tuberin respectively, function together within the cell and have an inhibitory effect on the mammalian target of rapamycin (mTOR), a protein kinase that influences cell growth and division through the regulation of protein formation.[4] Pathogenic mutations in TSC1 or TSC2 lead to over-activation of the mTOR pathway, which can cause growth of benign tumours (hamartomas) in various organs, such as the brain, kidneys, skin, heart, lungs and bones, these hamartomas being the clinical hallmarks of the disease.[5]

TSC is a multisystem disorder that can affect almost any organ in the body. The skin is commonly affected with lesions such as facial angiofibromatosis, hypomelanic macules, shagreen patches, forehead fibrous plaques and periungual fibromas.[3] However, the most serious morbidity is caused by lesions in the central-nervous, renal, pulmonary and endocrine systems.[6] Epilepsy is a common presenting symptom and medical problem in TSC and it is thought to arise secondary to cortical and subcortical tubers.[7] The majority of patients with TSC present with seizures during infancy, often with epileptic spasms, and many go on to suffer with intractable epilepsy throughout life.[7] Sub-ependymal giant cell astrocytomas (SEGAs) are slow growing benign tumours, seen in 5% to 20% of individuals with TSC.[8] As they grow adjacent to the foramen of Monro, they can cause clinical problems by blockage of cerebrospinal fluid pathways within the ventricular system leading to obstructive hydrocephalus.[8] More than 80% of TSC patients have kidney

angiomyolipomas. These lesions can haemorrhage which may be life-threatening or cumulative bleeds may lead to destruction of viable renal tissue and ultimately lead to renal failure.[9] Pulmonary lymphangioleiomyomatosis (LAM) occurs almost exclusively in female patients and they can present with progressive shortness of breath, recurrent pneumothoraces and deterioration in lung function.[10]

The causes of death in this group of patients have rarely been studied with the one published account from the Mayo Clinic appearing in 1991.[6] This study reported that the majority of patients died due to renal disease or SEGA lesions. We are conducting this study to investigate the causes of death in a more contemporary population of patients to investigate whether causes of mortality have changed over time or differ within a different healthcare system. The results of such a study may help clinicians and policy makers to decide where best to focus efforts and resources to reduce mortality in the future.

Methods

The Bath TSC clinic is a specialist supra-regional clinic and sees patients with TSC of all ages. We reviewed a database of all patients who had attended the Bath TSC clinic from 1981 to 2015 inclusive.

Of these patients, we identified 284 patients with a definite diagnosis of TSC, as defined by the International Tuberous Sclerosis Complex Consensus Group.[11] We reviewed the medical records, including medical notes, radiology images, and where applicable, death certificates and post-mortem reports, in order to determine the age and cause of death. Patients were confirmed to be either alive or deceased through clinic records or through GP records if not actively attending clinic. If the death certificate or post-mortem details were not present in the medical records, they were obtained via the hospital bereavement services, primary care facilities, or requested from the General Register Office. Additionally, details regarding patient demographics and clinical details were reviewed. Ethical approval was not required but all patient details were anonymised.

This is a clinic cohort in which there was heterogeneity in terms of administered investigations. For example, not all patients were administered psychometric tests in a consistent fashion, but some tests were requested and administered when an initial clinical screen of abilities identified areas of concern. We divided the clinic cohort into two groups: those with (“LD”) or without (“non-LD”) learning disabilities. Patients were

given these diagnoses of learning disability based on their abilities to understand new or complex information or to learn new skills, or their ability to cope or live independently, and with such inabilities having started before adulthood. Although these categorisations were made on the basis of clinical assessment rather than according to any measurement tool, they broadly concord with the definitions of learning disability defined by the UK Department of Health.[12]

Results

284 patients with a definite diagnosis of Tuberous Sclerosis Complex, attended the Bath TS clinic from 1981 to 2015 and all were included in this study. There were 149 (52%) patients with learning disabilities. The median age of LD patients was 25 years interquartile range (IQR) 15-36, and the median age of patients without LD was 28 years (IQR 17-43). There was no gender difference in this cohort.

The median follow up duration for all clinic patients was 8 years (IQR 3-17). Forty-one patients had a follow up duration of >20 years, 92 patients had a follow up duration of 10-20 years and 151 had a follow up duration of less than 10 years.

Eighteen patients (11 female and 7 male) in the clinic cohort died during this period. In two patients, the cause of death was considered not to be directly attributable to TSC. One patient died from ischaemic heart disease at age 80 years, and the other patient from pulmonary embolism, secondary to deep venous thrombosis of the leg at age 33 years. The pulmonary embolism was confirmed by CT scan and there was no evidence of LAM.

The age range of the 16 patients who died directly due to TSC was 17 to 60 years. Median age of death in this group was 33 years (IQR 26-46). (Figure 2) Seventy-one out of 284 patients in the clinic cohort where children aged 0-16 years.

In the mortality group, 13 out of 16 patients who died of causes directly related to TSC, had learning disability. Mortality was significantly more common in the LD group than the non-LD patients (9% vs 2%, Fisher exact test, $p = 0.02$, Table 1).

Death due to renal causes was seen in eight patients (6 female and 2 male). Three of these patients had chronic kidney failure and one of those three patients had polycystic kidney disease. Three died secondary to

acute haemorrhage from renal angiomyolipomas. One of those three patients had had kidney haemorrhage requiring multiple embolisations, one had bilateral multiple angiomyolipomas and diffusely abnormal kidneys. The remaining two patients died due to renal cell carcinoma.

In our clinic cohort, four deaths were attributed to sudden unexplained death in epilepsy (SUDEP), one of which occurred in a case with no identified learning disabilities. SUDEP was defined according to the criteria published by Devinsky et al.[13] Age at death was between 18 and 40 years. All four patients had developed epilepsy before the age of 16 years, and suffered from more than three generalised tonic-clonic seizures per year. Three patients were on antiepileptic monotherarpy with carbamazepine, and one patient was on a combination of carbamazepine with clonazepam and also had a working VNS (vagus nerve stimulator) in situ at the time of death. None of these patients were identified as being in status epilepticus at the time of death but they were all assessed to have had an epileptic seizure immediately prior to death. In these cases, age at the time of death was between 18 and 40 years.

Pulmonary lymphangioleiomyomatosis (LAM) was the stated cause of death in two patients, both of whom were female. One patient, aged 17 years, had developed heart failure due to LAM lesions in the lung, and the second patient, aged 19 years, died in her sleep secondary to massive pulmonary haemorrhage.

One patient died at age 33 years due to a metastatic non-secreting neuroendocrine pancreatic tumour.

One patient died aged 26 years due to SEGA. He was referred to our service in 1989 and after neurosurgeons had already recommended a palliative approach because they assessed his SEGA to be inoperable at the time of diagnosis.

Discussion

This study, compared with the previously published report, provides important new insights into the causes of death in this patient group.[6] It confirmed renal causes as being the commonest cause of early death but it has also demonstrated that SUDEP is a significant and previously unreported risk in TSC. Patients with LD are significantly more likely to suffer premature death, and female patients are more at risk of death secondary to angiomyolipoma and LAM compared with males. In contrast

with the previous report, SEGA was an uncommon cause of death. There were no deaths during childhood.

This was a retrospective study design and was based on a clinic population, which creates the main limitation of this study and limits the degree of generalisability of its findings. Specialist clinics tend to ascertain more severe cases and we would anticipate this patient sample to have more medical issues and co-morbid factors than the overall population of people with TSC. The gender balance and prevalence of LD in our cohort, however, was similar to previously reported population based TSC cohorts, suggesting that this clinic population was not grossly dissimilar from the TSC population at large.[9, 14] A relative strength of this study, compared with the Mayo Clinic report, is that it relied not only on death certificates, but also on other sources, such as post-mortem examination and medical notes. Studies have shown that death certificates can be completed inaccurately and can be misleading when relied upon as the sole source of mortality data.[15]

In our series, the median age of death was 33 years (IQR 26-46). None of the cases died in the paediatric age range (<16 years). Although we would expect TSC complications become more prevalent with increasing age and possibly not to cause death in the paediatric age group, this finding contrasts with the earlier study, where 40% of the deaths were in children.[8] We believe that our study's finding of absent mortality in children and only single case of mortality secondary to SEGA reflects a period effect relating to increased awareness of this condition, improved surveillance within a specialist clinic population, and successful treatment within a specialist neurosurgical centre that has acquired significant experience in dealing with these mid-line tumours[8]. Although not reported from our clinic population, mortality in childhood in TSC may occur secondary to cardiac rhabdomyomas, which are TSC-related hamartomas that grow in foetal life and can cause a significant problem around the time of birth by such mechanisms as obstruction to blood flow or life-threatening arrhythmias. The cardiac rhabdomyomas tend to regress in size after the perinatal period and are unlikely to be a cause of death in cases ascertained through a TSC clinic, and this is a factor that would tend to bias downwards estimates of death in childhood in studies such as ours.[16]

In the surviving cohort, there was no significant gender imbalance (132 female and 134 male patients). The mortality in females was higher that of males (10 vs 6) but this difference was not statistically significant (two-tailed Fisher exact test for proportions of females vs males dying, P =

0.44). Female patients died predominantly secondary to renal and lung complications. Figure 3 shows cause of death by gender.

It is well known that pulmonary LAM occurs almost exclusively in women[10] and, therefore, it is not surprising that the two fatalities in this study secondary to LAM were females. One possible explanation for symptomatic LAM occurring almost exclusively in females is that LAM lesions are thought to express oestrogen and progesterone receptor proteins.[17] It is also noticeable that the two deaths associated with LAM occurred in women of child-bearing age, where there is exposure to higher levels of circulating oestrogen than at pre-pubertal or post-menopausal ages.[18] There are some suggestions that oestrogen-containing contraceptives can exacerbate pulmonary LAM lesions.[19,20]

In this study, six out of the eight patients who died from renal causes were female. One previous population-based study has shown angiomyolipomas to be slightly, but not significantly, more prevalent in women but the difference in prevalence is not so large as to explain the differential renal associated mortality between the genders.[9,21] It is possible that the differential mortality is explained by the fact that angiomyolipomas also express oestrogen receptors, thus making them more likely to grow to a dangerous size in the female population, but it might also be a chance finding given that it is a relatively uncommon cause of death in a moderately-sized study population.

Thirteen of the patients who died had learning disabilities. The increased risk of early mortality in LD patients has not previously been reported. LD is a recognised feature of TSC and seen in approximately 50% of patients, [22] and in our cohort, 52% had LD. The increased risk of early mortality in the LD population of TSC patients is plausible for several reasons. Firstly, the LD population may be prone to having more hamartomas than non-LD patients. One study has previously reported that patients with LD have more TSC related renal hamartomas.[23] Secondly, patients with learning disabilities are at much higher risk of epilepsy than patients without learning disabilities, and therefore also at higher risk of SUDEP.[7] Finally, patients with LD are less likely to be able to communicate symptoms to their carers and their complications may not come to medical attention until they are more advanced. Based on these findings, patients with learning disabilities merit regular and close surveillance in order to minimise the risk of premature death.

Death due to renal causes was the commonest cause of death in this group. Three patients died due to renal bleeding from angiomyolipomas

without any preceding history of renal failure. Three died due to renal failure secondary to extensive angiomyolipoma formation and recurrent bleeds. Two patients died secondary to renal cell carcinoma. These findings support the need for regular surveillance of this population for the development of potentially fatal renal lesions.

In our study four deaths were attributed to SUDEP. No SUDEP cases have previously been reported in TSC. Deaths due to status epilepticus have been reported in TSC.[24]

All patients had multiple risk factors for SUDEP. They were adults aged between 18 and 40 years at the time of death. SUDEP has been reported to be four times more likely in adults compared with children, and the peak age categories at time of death from this cause are between 20 to 40 years.[25] All four patients had developed epilepsy before the age of 16, suffered from multiple generalised tonic-clonic seizures per year and were on treatment with carbamazepine. Three of these patients had learning disabilities. Previous reports have linked all these factors to SUDEP.[26] It is also possible in TSC patients that residual cardiac rhabdomyomas may predispose patients to cardiac arrhythmia in the context of an epileptic seizure. Interestingly, two post-mortem reports of the SUDEP cases reported the presence of cardiac rhabdomyomas on post-mortem examination. These patients were being monitored in the hospital at the time of death and their ECG monitoring showed changes just seconds before their death. The ECG changes and the presence of rhabdomyomas suggest that the cause of death could be cardiac rather than cerebral.

One patient died due to a metastatic pancreatic tumour. Pancreatic tumours have been reported in individuals with Tuberous Sclerosis Complex and the mTOR pathway appears to be activated in pancreatic cancer cells.[27, 28]

We have recently seen two TSC patients with pancreatic tumours who are under investigation and treatment. It is incorrect to assume that all pancreatic lesions in individuals with TSC are benign and necessitate no treatment. All TSC patients should probably have intermittent abdominal MRI scans to check for pancreatic tumours as these tumours are not always easily picked up during kidney US scan surveillance. The International Tuberous Sclerosis Complex Consensus Group recommends abdominal MRI scan to detect pancreatic tumours.[11]

Eight patients received mTOR inhibitors such as rapamycin and everolimus. Two patients received this treatment due to SEGA, one due to epilepsy, 4 due to angiomyolipomas and one due to pancreatic tumour. None of the patients who died in this cohort had ever received any mTOR inhibitors. mTOR inhibition has only recently become available for TSC patients in the UK and it is impossible to know if use of mTOR inhibitors would have had any impact on the mortality rate reported in this observational study.

In conclusion, this study has emphasised that renal disease is a major cause of mortality in TSC patients. We believe that lifelong surveillance of renal lesions, to enable appropriate management of potentially life-threatening complications, is warranted. The study has revealed also that SUDEP is a significant cause of mortality in these patients. Patients and carers should be warned about this risk. In our cohort, LD patients were at significantly greater risk of early mortality and this indicates the need for greater vigilance in these patients for the development of lesions, and indeed of symptoms that they may not be able to communicate clearly to their carers. Female patients are particularly vulnerable to pulmonary and renal disease. The mortality from pulmonary disease in young women provides a strong argument that all post-pubertal female TSC patients should be screened for LAM and treated appropriately. Finally, pancreatic lesions, although rarely reported in TSC, are a reported cause of mortality and they should be looked for in TSC patients, not just by means of abdominal ultrasound, which is a relatively insensitive investigation, but also with intermittent abdominal magnetic resonance imaging, as is stated within the International Tuberous Sclerosis Complex recommendations.[11]

Potential Conflict of Interests

Nothing to report.

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Figure 1: Shows the age, gender, and year of death of those patients who died from causes related to TSC.

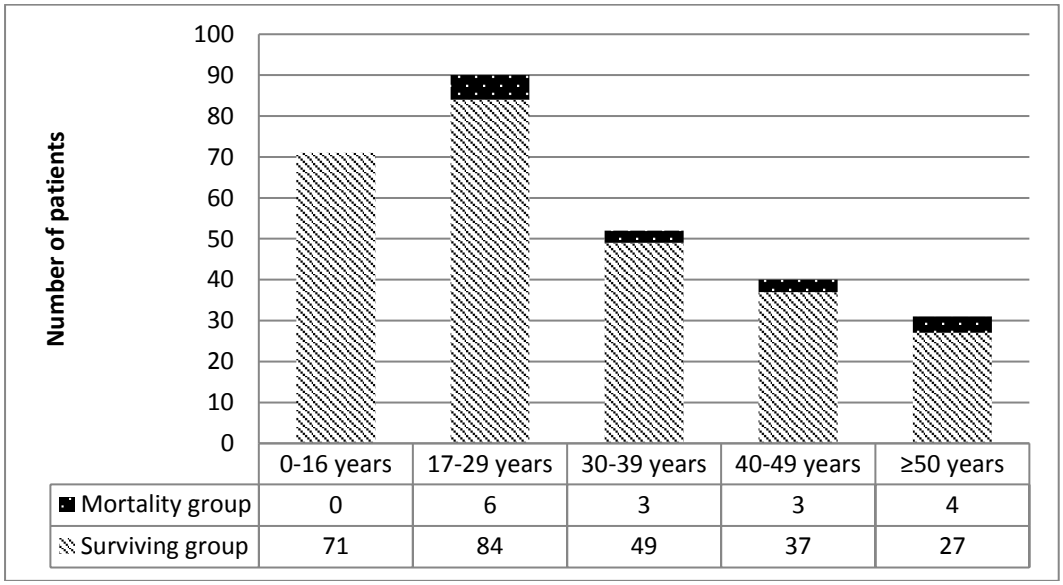

Figure 2: Age category in 2015 of surviving patients or age at death in patients within the mortality cohort.

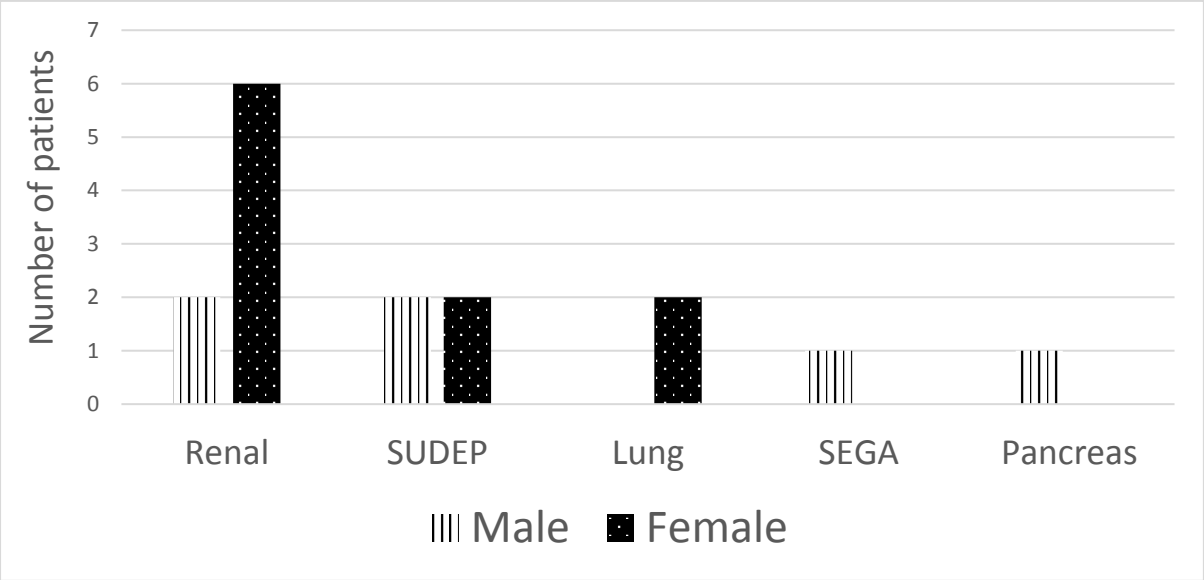

Figure 3: Causes of death and patient gender

	Dead	Alive	Totals
Patients with LD	**13**	**135**	**148**
Patients without LD	**3**	**131**	**134**
Totals	**16**	**266**	**282**

Table 1: Comparison of mortality in patients with learning disabilities and patients without learning disabilities; two-tailed Fisher exact test, P=0.02.