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CASE REPORT

R. W. Byard,[1] *P.C. Blumbergs,*[2] *and R. A. James*[1]

Mechanisms of Unexpected Death in Tuberous Sclerosis

ABSTRACT: Tuberous sclerosis complex is a protean autosomal dominant disorder characterized by multifocal tissue lesions arising from defects in cellular migration, proliferation, and differentiation. It has an association with sudden death. In the current study, review of all cases of sudden death due to tuberous sclerosis was undertaken at the Forensic Science Centre in Adelaide, Australia from 1991 to 2001, in addition to an analysis of cases from the literature. There were two local cases where unexpected death had occurred in individuals with known tuberous sclerosis, involving a 31-year-old male (epilepsy), and a 24-year-old female (massive hemorrhage into a renal angiomyolipoma). Fatal mechanisms in cases of tuberous sclerosis may be associated with underlying cardiovascular, renal and cerebral abnormalities. Sudden death may be due to cardiac arrhythmia, epilepsy, and intra-tumoral hemorrhage with additional complications including cardiac outflow obstruction, obstructive hydrocephalus, aneurysm rupture, and spontaneous pneumothorax. An awareness of the highly variable tissue manifestations of tuberous sclerosis and the mechanisms that may be responsible for death is necessary to establish correctly the diagnosis in occult cases (possibly with molecular confirmation), and to chart accurately organ changes in individuals with established disease.

KEYWORDS: forensic science, epilepsy, rhabdomyomas, sudden death, tuberous sclerosis complex

Tuberous sclerosis is an inherited disorder characterized by abnormalities of cellular migration, proliferation and differentiation in a wide variety of tissue and organ systems (1). First described by von Recklinghausen in 1862, it is distinguished clinically by the triad of epilepsy, mental retardation and facial angiofibromas (so-called abdenoma sebaceum) (2). The birth incidence is one in 6000 with the majority of cases being new mutations (3). Almost every tissue has been associated with abnormal manifestations in patients with tuberous sclerosis except for skeletal muscle (3–5). In addition to an overall reduction in life span, individuals with tuberous sclerosis may suffer sudden death. The following study was undertaken to investigate the occurrence and possible lethal mechanisms of sudden death from tuberous sclerosis in the general population.

Materials and Methods

The files of the Forensic Science Centre in Adelaide, South Australia were examined over an 11-year period from January 1991 to December 2001 for cases where death had been attributed to tuberous sclerosis. The Forensic Science Centre provides autopsy services to the State Coroner for the State of South Australia, Australia, which has a population of approximately 1.5 million people. Over 90% of the state's coronial autopsies are performed at the Centre.

[1] Forensic Science Center, Adelaide, Australia.
[2] Neuropathology Laboratory, Institute of Medical & Veterinary Science, & University of Adelaide, Adelaide, South Australia, Australia.

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Results

Two cases were identified out of a total of 10,709 autopsies performed over the study period (0.02%).

Case 1—A 31-year-old male with known tuberous sclerosis was found dead at his home. He had a history of mental retardation and poorly-controlled epilepsy. At autopsy, facial angiofibromas, renal angiomyolipomas and cysts, multiple cortical tubers, subependymal nodules and a subependymal giant cell tumor of the left periventricular region (Figs. 1–4) were identified. No rhabdomyomas were identified within the heart. Toxicological examination of blood demonstrated therapeutic levels of anticonvulsants phenytoin and primidone. Death was attributed to tuberous sclerosis with the fatal episode due to epilepsy related to multifocal cerebral abnormalities.

Case 2—A 24-year-old female with known tuberous sclerosis collapsed and was taken to a local hospital where resuscitation attempts were unsuccessful. At autopsy, the major findings were limited to the peritoneal and cranial cavities. The peritoneal cavity contained 800 mL of fluid blood associated with over 1 L of retroperitoneal hemorrhage on the right side. Further dissection revealed bilaterally enlarged kidneys with extensive intraparenchymal angiomyolipomas (Fig. 5). Marked hemorrhage had occurred into a large hamartoma within the right kidney. Scattered cortical tubers were present within the brain. No rhabdomyomas were identified within the heart. Death was due to massive hemorrhage into a renal angiomyolipoma.

Discussion

The clinical manifestations of tuberous sclerosis are quite variable with major diagnostic features including facial angiofibromas

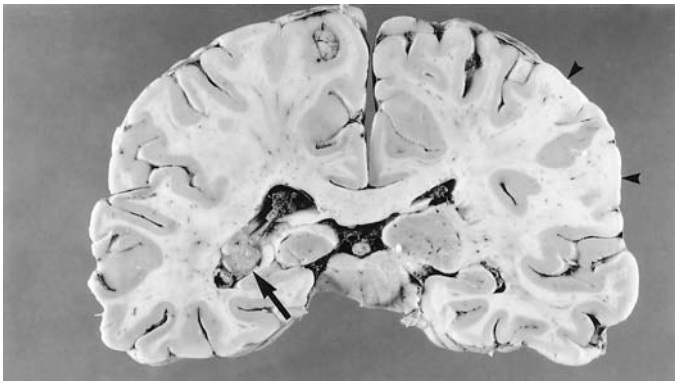


FIG. 1—*A coronal section of the cerebral hemispheres in Case 1 at the level of the pulvinar showing a left sided intraventricular tumor (subependymal giant cell astrocytoma) (arrow) and two cortical tubers of the right parietal lobe (arrowheads).*

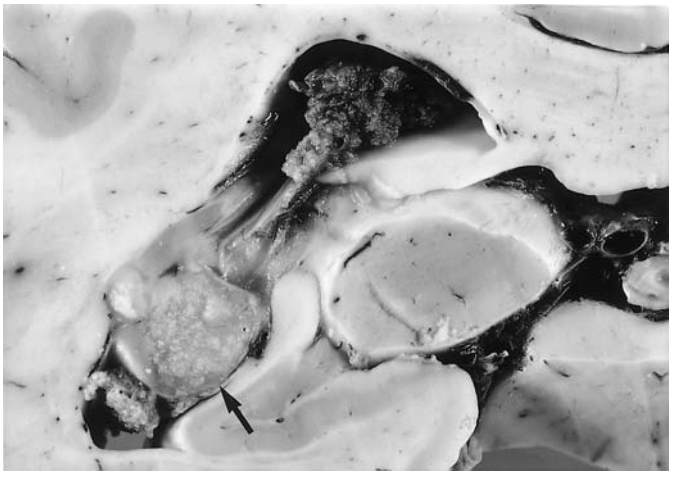
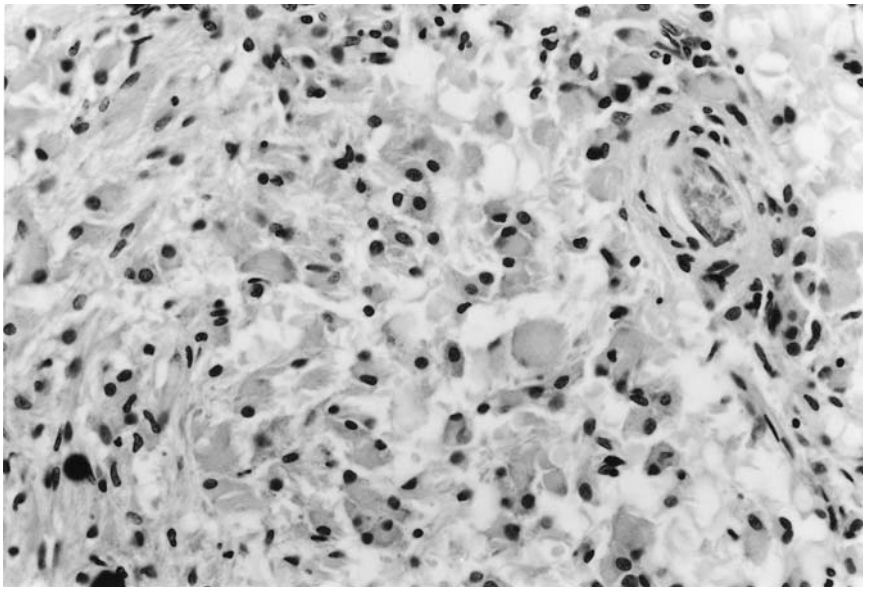


FIG. 2—*Close-up of the subependymal giant cell astrocytoma (arrow) in Case 1.*



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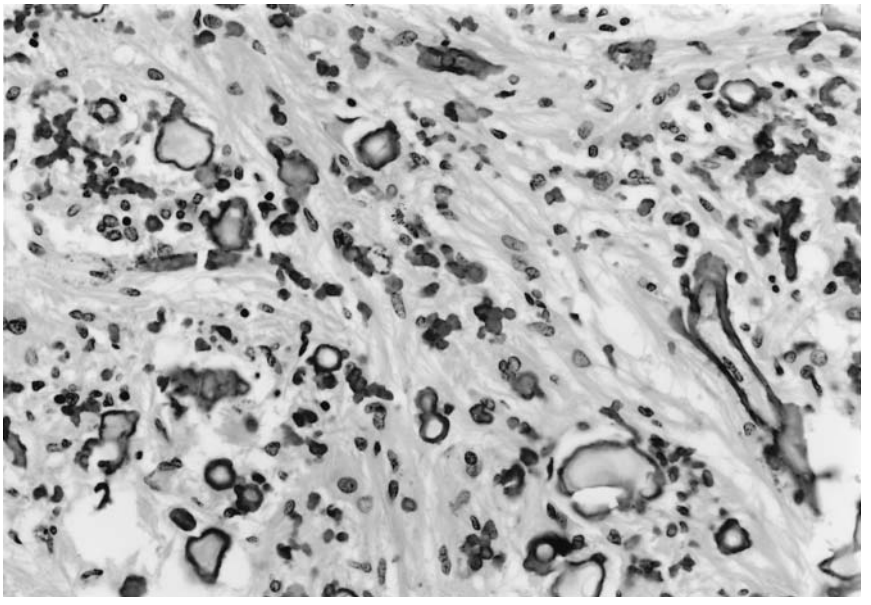

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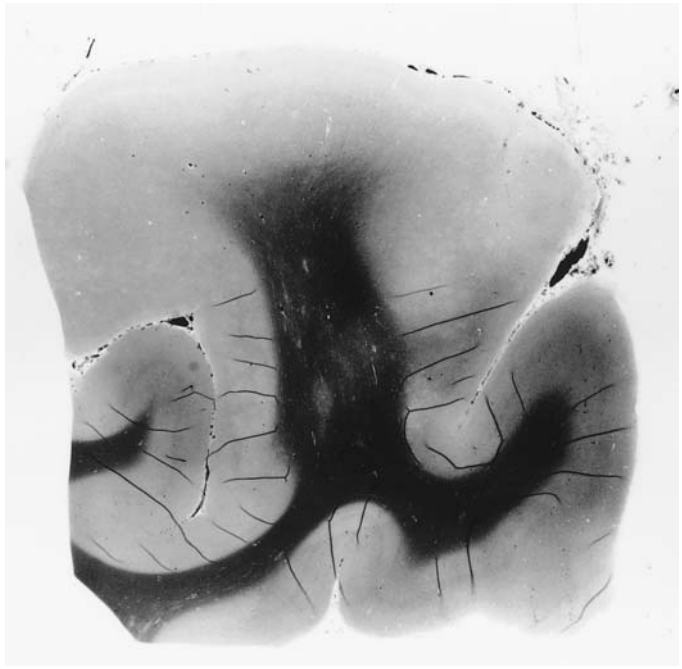
FIG. 3—*Histologic sections of the subependymal giant cell astrocytoma in Case 1 demonstrated characteristic disorganised aggregated round to oval, fusiform cells with abundant eosinophilic cytoplasm and eccentrically placed nuclei (A). Extensive microcalcification was also present (B) (Hematoxylin & eosin, × 250).*



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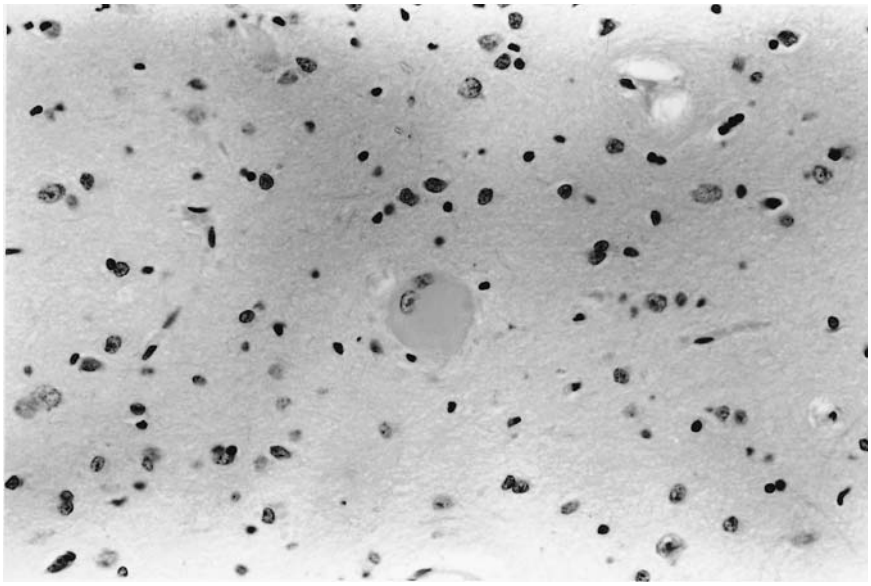

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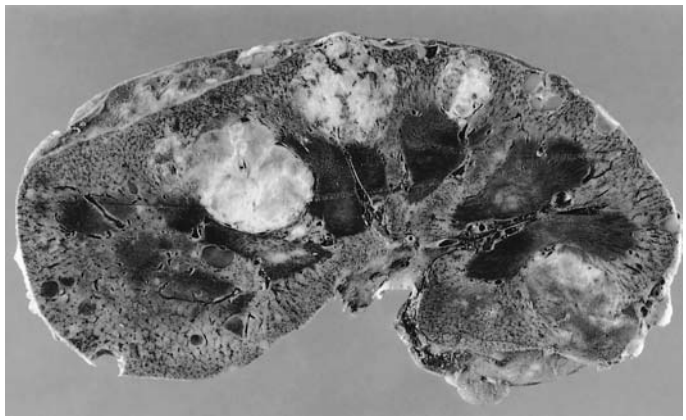
FIG. 4—*A wholemount section of a portion of cerebrum from Case 1 demonstrating expansion of a gyrus with blurring of the margin between grey and white matter due to a cortical tuber (A). (Weil, × 3). Histologically the tuber contained scattered large, bizarre, binucleate cells (B) (Hematoxylin & eosin, × 250).*

or forehead plaques, hypomelanotic macules, nontraumatic ungual or periungual fibromas, shagreen patches, cardiac rhabdomyomas, cortical hamartomas (tubers), subcortical glioneuronal hamartomas, subependymal nodules, subependymal giant cell astrocytomas (SEGA), nodular retinal hamartomas, retinal giant cell astrocytomas, renal angiomyolipomas and pulmonary lymphangiomyomatosis. Minor criteria include dental enamal pits, cerebral white matter radial migration lines, bone cysts, hamartomatous rectal polyps, gingival fibromas, non-renal hamartomas, retinal achromic patches, "confetti" skin lesions and renal cysts (1,6). Rare cases have also been reported with aortic and intracerebral aneurysms, and megacystis-microcolon-intestinal hypoperistalsis syndrome (7–9).

Tuberous sclerosis is an autosomal dominant disorder with a high degree of penetrance and a spontaneous mutation rate of 65 to 75% (4). Two tuberous sclerosis genes with a common phenotype have been identified: TSC1 on chromosome 9q34, and TSC2 on 16p13 (10). These are tumor suppressor genes responsible for the production of proteins hamartin and tuberin, respectively. While expression of these proteins has been demonstrated in neuroglial cells taken from cortical tubers (11) the exact nature of their interaction has not yet been ascertained (4).

An awareness of the nature and manifestations of tuberous sclerosis complex is important in forensic pathology to ensure that the diagnosis can be correctly established in occult cases presenting unexpectedly to autopsy (2), and to accurately record the manifes-



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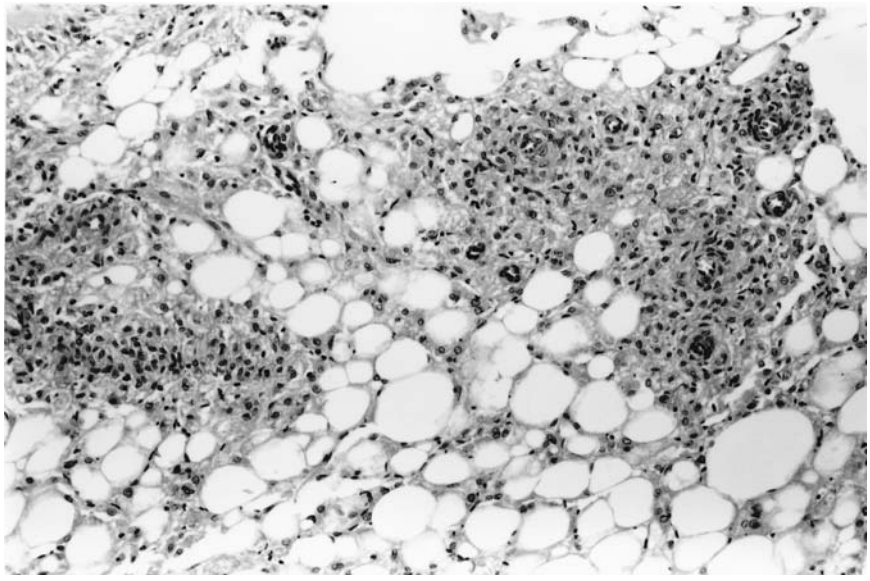

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FIG. 5—*Cross section of the enlarged left kidney in Case 2 demonstrating multifocal angiomyolipomas. The kidney weighed 457 g and measured 50 × 90 × 170 mm (A). Histologically the angiomyolipoma consisted of intermingled fibrovascular and mature adipose tissue (B) (Hematoxylin & eosin, × 200).*

tations of the condition in individuals with established diagnoses. In addition, given the heritable nature of cases, recognition of cases at the time of autopsy may be vital to ensure that tissues are taken to enable genetic characterisation if this is required.

It must be remembered that sudden death in individuals with tuberous sclerosis complex may be due to organic illnesses or accidents that are completely unrelated to the underlying disorder. The manifestations found at autopsy will then be purely incidental, as in the case of an apparently normal 13-month-old boy who died after ingesting soldering flux, but who was found at autopsy to have facial angiofibromas, cardiac rhabdomyomas and cortical tubers (2). When unexpected death does result from tuberous sclerosis, it may be due to a variety of mechanisms and these may be age-related. For example, cardiac rhabdomyomas tend to regress with age and pulmonary lymphangiomyomatosis is primarily a disorder of adult females (1,12,13). Sudden death may be due to cardiac, cerebral, renal and vascular causes (Table 1). Although patients with tuberous sclerosis complex have been shown to have reduced survival compared with the general population (14), the exact incidence of sudden death cannot be determined by this study because not every death would necessarily be the subject of a coronial autopsy.

TABLE 1—*Factors which may be involved in unexpected death in tuberous sclerosis.*

Intracerebral	i) epilepsy
	ii) intratumoral hemorrhage
	iii) obstructive hydrocephalus
Cardiac	i) arrhythmia
	ii) outflow obstruction
Renal	i) intratumoral hemorrhage
Vascular	i) aortic aneurysm
	ii) intracerebral aneurysm
	iii) peripheral aneurysm
Pulmonary	i) pneumothorax
	ii) chylous effusions

Cardiac manifestations resulting in sudden death arise from rhabdomyomas. These are the most common primary cardiac "tumor" in childhood and consist of aggregates of vacuolated "spider" cells with large clear cytoplasm and eccentrically or centrally-placed nuclei (15). They are usually multiple, varying in size from 1 mm to 10 cm, have a predilection for the ventricles and tend to project into the cardiac cavity (12). Sudden death may result from

rhythm disturbance and an association with Wolff-Parkinson-White syndrome has been documented (3). Outflow obstruction and valvular distortion may occur and a variant form has also been reported where multifocal rhabdomyomas may be found throughout the ventricles and atria. This caused the sudden death of a 13-year-old boy and was termed "rhabdomyomatosis" (16).

Sudden death due to intracranial pathology in tuberous sclerosis is most often related to epilepsy, one of the cardinal clinical manifestations. The pathological diagnosis is, however, one of exclusion, made when there is a supportive clinical history, with typical neuropathological findings such as cortical hamartomas, subependymal nodules, focal cortical dysplasia and subependymal giant cell astrocytomas, and no other likely causes of death identified at autopsy, as in Case 1. The spinal cord is only rarely involved (1). Sudden death due to epilepsy may be more likely if the epilepsy is poorly controlled, or if other precipitating factors such as infection are present (17). Other intracranial causes of sudden death may include spontaneous hemorrhage into a subependymal giant cell astrocytoma, obstructive hydrocephalus, and cerebral aneurysm rupture (1,9,18,19).

Spontaneous hemorrhage into a renal angiomyolipoma was responsible for the death of a young woman in Case 2. Angiomyolipomas are composed of an admixture of smooth muscle cells, adipose tissue and abnormal blood vessels. They are present in 80% of patients with tuberous sclerosis and are bilateral in 75% of cases. Spontaneous hemorrhage is a known complication of angiomyolipomas, more commonly associated with larger lesions (1,20). While a Mayo Clinic study found renal disease to be the most common cause of death in adults with tuberous sclerosis, most deaths were from renal failure and not from hemorrhage (14).

Vascular abnormalities have been uncommonly reported in patients with tuberous sclerosis and consist of aortic, intracranial and peripheral arterial aneurysms (8). Histologic abnormalities of arteries have included reduction and fragmentation of elastic fibres, with an increase in glycosaminoglycans resulting in ectasia, aneurysms, and vascular obstruction. There may also be fibrointimal proliferation of intracerebral vessels producing a moyamoya effect (9). Aneurysmally dilated vessels with abnormal walls are at risk of spontaneous rupture (8), possibly with rapid and fatal consequences. Involvement of the lungs is rare, occurring in 1 to 6% of cases, usually in females aged between 20 and 40 years. Although the clinical manifestations of pulmonary involvement are usually chronic, spontaneous pneumothoraces and chylous effusions may precipitate acute respiratory failure (1).

In conclusion, individuals with tuberous sclerosis are at increased risk of sudden death at all ages from a variety of mechanisms, associated with a range of underlying cardiovascular, renal and cerebral abnormalities. Although the precise etiology of the manifestations of tuberous sclerosis complex is not well understood, sudden death may be due to cardiac arrhythmia, epilepsy, and intra-tumoral hemorrhage. Additional problems may include aneurysm rupture, cardiac outflow obstruction, obstructive hydrocephalus and spontaneous pneumothorax. The autopsy assessment of such cases should, therefore, include careful examination for diverse lesions from a number of systems as these may have had an integral role in the terminal episode.

Acknowledgments

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Additional information and reprint requests:
Professor Roger W. Byard
Forensic Science Centre
21 Divett Place
Adelaide 5000, Australia
E-mail: byard.roger@saugov.sa.gov.au