

Annotations

Diagnosis of tuberous sclerosis

Tuberous sclerosis was first clearly documented in 1880 by Bourneville (hence Bourneville's disease or epiloia) who described the typical pathological features—areas of sclerosis and other areas of tuber like growths at postmortem examination—in patients with mental retardation and fits.¹ For years the disease was only suspected in those suffering from mental retardation and fits but it is now known to occur in individuals of normal intelligence both with or without fits. The classic paper by Bunday and Evans brought this to attention by confirming that the disease is dominantly inherited often from unsuspecting parents who nevertheless have signs of the disease.² The incidence was thought to be one in 100 000 but the best estimate³ has been recently updated (R H Lindenbaum, personal communication) to suggest one in 10 000. Mental retardation is thought to affect 50% of individuals with fits occurring in about 80%.

Clinical manifestations

The disease is now known to cause a plethora of abnormalities in a variety of organs.⁴

SKIN

The classic white patches are ash leaf in shape: these are often only seen in a dark room with an ultraviolet lamp and are the most common early sign.* Unfortunately 2–3 per 1000 of apparently normal newborn babies also show these patches.⁵ Depigmented lesions may affect the hair, eyebrows, eyelashes, or even iris. The facial lesions are histologically angiofibromas, not adenoma sebaceum as at first thought. Angiofibromas affect the cheeks, nasal folds, and chin but often spare the upper lip: they are rarely present before 2 years of age and may not occur until after puberty, if at all. The forehead fibrous plaque (a smooth patch of slightly raised skin with a reddish discolouration) is common and can be the first sign of the disease.⁶ Shagreen

patches usually occur from puberty and are leathery discoloured patches predominantly on the trunk, often in the lumbar region. Cafe-au-lait patches are not a sign of tuberous sclerosis.⁷ Fibromas most often affect the nails of both hands and feet, causing deep grooves, but can also occur in the gums around the teeth. The teeth can also be pitted.⁸

NEUROLOGY

Fits are the most common presenting symptom and most often begin in the first year of life. They can be partial (focal) or generalised tonic-clonic but are frequently infantile spasms where up to 20% of cases are due to tuberous sclerosis.⁹ Mental retardation is extremely rare without fits and usually becomes apparent in the first year of life. The fits are often resistant to treatment but control should be attempted.

The intracranial lesions are astrocytomas on histological examination and are usually benign, often calcifying. They characteristically line the lateral walls of the lateral ventricles but they can be found in the cerebrum and cerebellum, normally in association with more typically sited lesions. Obstruction at the foramen of Monro can cause hydrocephalus. Infrequently malignant giant cell astrocytomas occur: these are thought to enhance with contrast injection on computed tomography.¹⁰ The incidence of intracranial lesions is high even in asymptomatic patients and the advent of cranial computed tomography allowed easier early diagnosis in those presenting with fits. Not all paraventricular calcification is due to tuberous sclerosis but the multiple discreet nodular areas of calcification are fortunately fairly typical. A very early scan (the first six months of life especially) is not always reliable and may need to be repeated: up to 10% are normal initially. Transfontanellar cranial ultrasound scanning can be helpful even showing signs before they are visible on a computed tomogram,¹¹ but the reliability of this test is not yet certain. The place for scanning by nuclear magnetic resonance is not yet established but the demyelinated areas would be expected to show up more often: they are not, however, diagnostic but might perhaps relate to the severity of retardation.

Mental retardation is often severe with no verbal

*A hand held ultraviolet light costing approximately £12 is available from the secretary of the Tuberous Sclerosis Association, Mrs Janet Medcalf, Little Barnsley Farm, Catshill, Bromsgrove, Worcester B61 0NQ, from whom an illustrated medical leaflet will soon be available.

communication and appreciable autistic features making caring difficult. By adolescence there can be a clear cut improvement in the autistic features but behaviour disturbance in a fully grown mobile but non-communicating young adult with tuberous sclerosis can be the biggest problem for many parents.

EYES

Retinal phakoma are astrocytomas and are most easily seen when they calcify, appearing like great white tumours in any part of the retina. They are therefore best looked for in dilated eyes, preferably by indirect ophthalmoscopy: they can be mistaken for retinoblastoma in young children, and when this diagnosis is considered the child should be examined for other signs of tuberous sclerosis to prevent unnecessary enucleation. It is extremely uncommon to find retinal phakomas as the only sign of tuberous sclerosis.

HEART

The disease can also cause cardiac rhabdomyomata, which are now known to be much more common than previously thought.¹² They are visible on echocardiography but are more easily seen in children than adults both for technical reasons and because they can reduce in size with age. Overt arrhythmias are uncommon, but the rhabdomyomata can cause cardiac failure in infancy. It is quite possible that all cases of cardiac rhabdomyomata are due to tuberous sclerosis but this has yet to be demonstrated.

KIDNEY

Renal cysts (bilateral) can cause infantile polycystic disease. Angiomyolipomas also occur in the kidney more often in adults than in children.¹³ When multiple they are diagnostic. Renal failure is rare and usually due to cysts.

BONES

Bony changes include cysts, periosteal new bone, and areas of sclerosis, but they are rarely symptomatic.¹⁴ They are usually found in those in whom the diagnosis is obvious clinically.

Diagnosis

Making the diagnosis of tuberous sclerosis in an individual is therefore dependant on careful clinical evaluation (angiofibromas and unguinal fibromas are probably diagnostic) including ultraviolet light with special investigations (cranial computed tomography, indirect ophthalmoscopy, and less frequently renal ultrasound and echocardiography)

Table *Diagnostic features of tuberous sclerosis**

<i>Definitive diagnosis (primary features— only one required)</i>	<i>Presumptive diagnosis (secondary features— two required)</i>
Classical shagreen patches	Hypomelanotic macules
Ungual fibroma	Gingival fibromas
Retinal hamartomata	Bilateral polycystic kidneys
Facial angiofibromas	Cardiac rhabdomyoma
Subependymal glial nodules (on computed tomography)	Cortical tuber (histological)
Renal angiomyolipomata	Radiographic 'honeycomb' lungs
	Infantile spasms
	Myoclonic, tonic, or atonic seizures
	First degree relative with tuberous sclerosis
	Forehead fibrous plaque
	Giant cell astrocytoma

*Modified from Gomez.¹³ This is for guidance only, clinical judgment is still often required.

when necessary. Gomez produced diagnostic criteria,¹³ which require modification (table): these are supposed to be a helpful guide not a rigid list of rules. Rarely, for instance, an obligate carrier has only a 'secondary' sign, such as white patches, whereas the presence of white patches in a young child with fits does not guarantee tuberous sclerosis: confirmation, often by a cranial computed tomogram would be wise.

Genetics

With the discovery in 1987 that the gene for tuberous sclerosis is on chromosome 9,¹⁵ linked to the gene locus for the ABO blood group, tuberous sclerosis could be said to have come of age. The gene was provisionally assigned to 9q34 at the eighth international conference on human gene mapping but this has not been confirmed by studies in the United States of America where heterogeneity was suggested¹⁶; however, no clinical evidence for this has yet been found. The variability of expression of the disease can be extreme but often occurs within a family, the variability affecting all clinical features. Linkage has now been shown to a DNA polymorphism detected by v-abl¹⁷ and an antenatal diagnosis performed using this marker.¹⁸ More recent data suggest that this is not a sufficiently close marker for reliable antenatal detection,¹⁹ but the evidence from the United Kingdom still suggests that the tuberous sclerosis gene locus is on chromosome 9 at q34. With the discovery of more tightly linked markers, antenatal diagnosis will become a reality. Blood should be stored now for later analysis from any relevant family member, affected

or unaffected, who is likely to die, and where antenatal diagnosis may later be required.

Familial cases are the minority and up to 80% of cases are new mutations occurring to normal parents. What investigations are required to exclude the diagnosis in parents? Clearly a detailed dermatological examination, including ultraviolet light examination, is essential as is ophthalmic examination which is non-invasive. Sporadic reports suggest that cranial computed tomography may pick up further cases^{20 21} but even nuclear magnetic resonance imaging and other detailed investigation may fail to detect any evidence of disease in apparent obligate carriers.²² This may represent germinal mosaicism rather than incomplete penetrance. The risk of recurrence of 1–2% in those normal on full investigation is probably much the same as for those normal on skin and eye examination only, but it is still perhaps wise to request cranial computed tomography.

Siblings of apparently isolated cases should be encouraged to have skin and eye examinations before being told that there is no recurrence risk because their parents are normal. Occasionally the only sign of disease is a fibroma of the nail. A single ash leaf patch probably remains the most common ambiguous clinical sign. As an incidental finding it should be ignored—in isolation it is not diagnostic but it is considered by some to be sufficient to make the diagnosis in an individual with a first degree relative with tuberous sclerosis. An intragenic marker might help to clarify the situation on those occasions where signs are in doubt and this may be available within the next decade as details of the gene locus are unravelled.

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