suppression of growth hormone concentrations. However, the fine line between the mitogenic and metabolic effects of IGF-I needs to be carefully defined. In IDDM it could be argued that reductions in growth hormone hypersecretion, insulin dose, and glycated haemoglobin brought about by rhIGF-I might lead to a reduced risk for microangiopathic complications, but in vitro evidence implicates tissue production of IGF-I in the development of these complications. Future studies will have to proceed cautiously, but the application of the effects of rhIGF-I, its analogues and the IGFBPs in the treatment of diabetes and catabolism will prove to be an exciting and innovative field of research.

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Tuberous sclerosis

Tuberous sclerosis is the commonest dominantly inherited condition causing epilepsy and mental handicap. It has attracted considerable research interest in the last decade and in this review we look at some of the new information on epidemiology, presentation, diagnosis, management, prognosis and genetics, relating clinical information to the discovery that the tuberous sclerosis genes are tumour suppressor genes.

Epidemiology

The clinical expression of tuberous sclerosis is so variable that the true prevalence of the disease remains unknown. Two observations suggest the birth incidence is considerably higher than previously estimated: (a) population based studies consistently identify a higher prevalence of the disease in childhood[1 2] and (b) studies of children with the disease are particularly likely to be biased by under ascertainment of mildly affected cases. Because the prevalence of learning difficulties in tuberous sclerosis is now recognised to be lower than previously documented,[3 4] we predicted the true birth incidence to be at least 1/6000.[3] A recent Swedish study found a prevalence of 1/6800 among children aged 11–15 years.[5]

Presentation

The majority of individuals with tuberous sclerosis who present in childhood will have epileptic seizures and the disease should be considered in every child presenting with a seizure. Infantile spasms, complex partial and myoclonic seizures are the commonest seizures encountered. A significant number (10%) of children presenting with infantile spasms will have tuberous sclerosis[6] and the diagnosis is important as it will influence treatment (see below). Learning difficulties or autistic behaviour without seizures are rarely due to tuberous sclerosis.

A few children will present with skin lesions[7] and other children will be seen because of the complications of cardiac rhabdomyomas[8] or polycystic kidney disease.[9] Cardiac rhabdomyomas cause their major problems in the perinatal and neonatal period and are associated with hydrops fetalis, heart failure, murmurs, arrhythmias, and Wolff-Parkinson-White syndrome. At least 80% of children presenting with cardiac rhabdomyomas will have tuberous sclerosis.[8] The renal cystic disease of tuberous sclerosis is indistinguishable clinically from autosomal dominant polycystic kidney disease and usually presents in infancy with palpable abdominal masses, haematuria, and/or hypertension. The two conditions are thought to be

distinguishable histologically.[7] We have seen one child who presented with a squint and this has been reported by others.[10]

A significant number of individuals will not come to medical attention until a more severely affected family member is identified. A small number of adolescents and young adults will present with complications of other visceral lesions such as renal angiomyolipomas,[11] giant cell astrocytomas,[7] or rarely pulmonary lymphangiomyomatosis.

Diagnosis

The diagnosis of tuberous sclerosis will remain a clinical judgment until DNA techniques allow screening for gene abnormalities (see below). The criteria currently employed for gene linkage studies have been modified from Gomez[7] and are outlined in the table. Clinical features which should alert the physician to the possibility of the disease in an infant include multiple hypomelanic macules (best seen with an ultraviolet lamp in a darkened room), a forehead fibrous plaque, a shagreen patch, and a retinal astrocytoma. Facial angiofibromas occur from about the age of 4 years, while ungual fibromas and multiple bilateral renal angiomyolipomas are more likely to present at or after puberty.

The most useful imaging modalities are cranial computed tomography or magnetic resonance imaging (MRI), echocardiography in a child, and abdominal ultrasound. Cranial computed tomography is useful in detecting the pathognomonic calcified subependymal glial nodules, while MRI is more accurate at identifying the number and location of cerebral cortical and subcortical lesions.[12 13] The appearances of the latter are not always pathognomonic. Cranial computed tomography and MRI can be normal in infancy but abnormal later and cranial imaging (computed tomography and MRI) is normal in about 5% of older affected individuals even in the presence of seizures.[12] MRI can be normal when computed tomography is not and vice versa. Echocardiography is most sensitive in early childhood and particularly under 2 years when more than 50% will have rhabdomyomas.[8 14] Abdominal ultrasound can detect polycystic kidney disease in infancy but is also helpful in adolescence when 30–50% will be expected to have renal and/or hepatic hamartomas.[11 15]

Management

The important issues in the management of individuals and families with tuberous sclerosis are (a) treatment of seizures, (b) handling of learning disorders and behaviour difficulties, (c) surveillance for and management of other complications, (d) giving a prognosis in individual cases, and (e) genetic counselling.

SEIZURES

It is not known whether early and effective treatment of seizures will reduce the risk of severe learning difficulties in tuberous sclerosis but while this possibility exists we believe that infants who present with seizures, especially infantile spasms, should be considered an emergency. Evidence is accumulating that infants with tuberous sclerosis who present with infantile spasms can respond at least as favourably to treatment with vigabatrin[16 17] as to more conventional steroid treatment. Long term follow up of the effects of vigabatrin are not available and optimal duration of treatment has yet to be defined. A response to vigabatrin is usually evident within 2–3 days and a reasonable starting dose is 50–100 mg/kg/day increasing to 150 mg/kg/day if required. Transient drowsiness is common on this regimen. Our protocol for steroid usage is 60 mg of oral prednisolone/day for a minimum of 14 days, followed by a reducing dosage. The presence of polycystic kidney disease might in theory make the risk of systemic hypertension with steroids a greater problem and careful monitoring is required. Nitrazepam and sodium valproate are also useful for infantile spasms. Seizures in infancy and older children with tuberous sclerosis should be treated conventionally with carbamazepine, sodium valproate, phenytoin, and vigabatrin for partial seizures and sodium valproate for generalised and myoclonic seizures. We rarely recommend phenobarbitone, clobazam, or clonazepam at any age because of their tendency to exacerbate behaviour problems in tuberous sclerosis. Experience is limited with both lamotrogine and gabapentin, but both may prove to be useful.

Does surgery have any place in the management of intractable epilepsy in tuberous sclerosis? New information suggest that it might if ictal electroencephalographic (EEG) discharges clearly correlate with a prominent cerebral lesion. In a study of nine patients with a mean follow up period of 35 months, cortical resection or lesionectomy led to complete seizure control in six (two without medication) and to a greater than 80% reduction in seizure frequency in two. Five of those who did well had additional cortical tubers and four had multifocal or generalised EEG abnormalities preoperatively. This improvement arose despite multifocal abnormalities on neuroimaging.[18] Callosotomy may also be helpful in those with severe drop attacks.

BEHAVIOUR

Behaviour disorders are common in tuberous sclerosis in the presence of seizures[19] especially if these are poorly controlled and improvement in seizure control can help behaviour.[20] Autism is recognised as a significant behaviour[21] but hyperactivity is also problematic and the two do not always occur together. Self injurious behaviour can be associated with anticonvulsants especially benzodiazepines and sleep disorders are common.[19] Psychological support, attention to communication disorders, and an appropriate social and educational environment especially for those with severe learning disorder can be invaluable.

SKIN

The cutaneous lesions of tuberous sclerosis are usually asymptomatic, although facial angiofibromas and ungual fibromas can cause complications with bleeding after minor trauma and in some individuals they represent a significant

Current diagnostic criteria used in tuberous sclerosis

Primary diagnostic criteria
Facial angiofibromas
Periungual fibromas
Calcified retinal astrocytomas
Multiple subependymal glial nodules
Multiple cortical tubers
Possible additional primary diagnostic criteria
Multiple bilateral renal angiomyolipomas
Forehead fibrous plaque
Shagreen patch
Diagnostic criteria with an affected first degree relative
Subependymal giant cell astrocytoma (histologically proved)
Cardiac rhabdomyomas (histologically proved or echocardiographic evidence in childhood)
Single cortical tuber
Single retinal astrocytoma
Secondary diagnostic criteria (two or more needed for diagnosis)
Typical hypomelanic macules
Bilateral polycystic kidneys
Radiographic honeycomb lung (due to pulmonary lymphangiomyomatosis)
Single cardiac rhabdomyoma or renal angiomyolipoma

cosmetic problem. The best results from treatment appear to be with laser therapy[22] but dermabrasion and cautery can also be effective and are more readily available in Britain.[23] Argon laser or tunable dye laser is thought to be best for angiomatous lesions while a carbon dioxide laser may be best for the more fibrous lesions. The best age for treatment and the recurrence risks are not known.

CARDIAC

Spontaneous resolution of cardiac rhabdomyomas occurs with time,[8 14 24] and the mainstay of treatment for heart failure and arrhythmias is medical. Cardiac rhabdomyomas have been successfully resected and this option should be considered in neonates with obstructive heart failure that is unresponsive to medical treatment. In Wolff-Parkinson-White syndrome the arrhythmias may become less troublesome with time even if the electrocardiographic evidence of pre-excitation remains.

RENAL

Angiomyolipomas are the main hamartoma affecting the kidney in tuberous sclerosis and are well seen on abdominal ultrasound where they are echogenic. Renal cysts can also be seen on ultrasound and are echolucent. Renal carcinomas rarely occur and are usually less echogenic than angiomyolipomas: where doubt exists computed tomography will demonstrate fat in an angiomyolipoma. Renal angiomyolipomas often bleed, presumably because they are highly vascular and deficient in elastin. Anecdotal evidence suggests that lesions that are 4 cm or larger are most likely to rupture[11 25] causing haemorrhage which if retroperitoneal can be life threatening. Haemorrhage into a lesion can cause pain, fever, and troublesome haematuria. Large symptomatic lesions should be evaluated by angiography and if possible selectively embolised.[25] The disease is often eventually bilateral so that partial nephrectomy or enucleation of a peripheral lesion may be appropriate in some cases but nephrectomy should if possible be avoided. We recommend five yearly renal ultrasound scans for all individuals with tuberous sclerosis and annual scans as soon as an abnormality is detected. End stage renal failure due to angiomyolipomas is uncommon in the absence of nephrectomy but the outlook after renal transplantation is good.[26] The polycystic kidney disease of tuberous sclerosis usually presents in infants and young children but can occur in adults and is managed conventionally. Multiple hamartomatous changes with cysts and small angiomyolipomas may represent a 'double hit' (see genetics section) at the earliest stage in renal development and may be associated with a higher risk of renal failure.

GIANT CELL ASTROCYTOMAS

Giant cell astrocytomas in individuals with tuberous sclerosis commonly obstruct the exit of the third ventricle and present with vomiting, visual loss, headaches, ataxia, or a change in behaviour, but only occasionally with a deterioration in seizure control. They are a slow growing tumour and have been successfully removed neurosurgically so that they have a better outlook than ordinary astrocytomas with a giant cell component.[27] There is no convincing evidence that radiation treatment provides a better survival rate or reduces the likelihood of tumour recurrence. We do not recommend screening for these lesions as they tend to become symptomatic at an early stage and new lesions can occur within months of a previously clear cranial scan.

Prognosis

More than half of affected individuals are now recognised to have normal intellect.[3] Children with tuberous sclerosis who do not develop seizures in the first five years of life are very unlikely to develop learning difficulties but the earlier the onset of seizures the greater the risk of severe learning difficulties.[28] Developmental regression with onset of seizures and improvement with seizure control is commonly experienced and has been reported.[20] Males with the disease appear to have a greater incidence of early onset seizures including infantile spasms and they have a worse outlook for seizure control and cognitive development.[28] There is no reliable relationship between the findings on cerebral computed tomography or MRI and cognitive outcome.[12] While the risk is greatest with a high number of lesions, the smallest of lesions can be associated with severe learning difficulties and a large number of lesions can occur in a normal individual – especially a female.[29] Shepherd *et al* have outlined the cause of death among patients with tuberous sclerosis attending the Mayo Clinic and recorded a reduced survival curve compared with normal white Americans.[30] The excess mortality was due largely to status epilepticus, renal disease, or giant cell astrocytomas. The absence of adults with tuberous sclerosis in epidemiological studies may be due in part to the increased fatality from seizures in the past.

Genetics

Linkage of tuberous sclerosis to markers on chromosome 9q was first reported in 1987[31] but it soon became clear that there is genetic heterogeneity. The gene on chromosome 9 was called TSC1. Using tuberous sclerosis families in which data had excluded linkage to chromosome 9, Kandt *et al* revealed an important tuberous sclerosis locus on the proximal side of the polycystic kidney disease type 1 (PKD1) gene on chromosome 16p13.[32] The European chromosome 16 tuberous sclerosis consortium have since identified a gene designated TSC2 which is interrupted by all five deletions they detected at 16p13.3.[33] No significant phenotypical differences have been discovered between TSC1 and TSC2. The TSC2 gene produces a shortened 5·5 kb transcript which is widely expressed and its protein product, tuberin, has a region of homology to the GTPase-activating protein GAP3 which is a member of a family of proteins involved in regulation of cell proliferation and differentiation.[33] The reduced expression of TSC2 in affected individuals suggests that constitutional mutations in tuberous sclerosis are likely to be inactivating and that the gene is likely to behave as a tumour suppressor gene. The patchy focal nature of tuberous sclerosis associated lesions and the loss of heterozygosity that they exhibit[34] suggest that reduction to the homozygous state is required before cellular growth and differentiation become disordered – Knudson's 'two hit hypothesis'. A similar combination of inactivating constitutional and somatic mutations has been clearly demonstrated in retinoblastoma and neurofibromatosis type I. This would explain the increasing risk with age of hamartoma formation in tuberous sclerosis, as well as the occasional individual without other signs of the disease who develops a hamartoma commonly associated with it such as a renal angiomyolipoma. These individuals have had two somatic mutations and do not have an inherited constitutional mutation. The gene for TSC2 is so close to the gene for adult polycystic kidney disease that at least one individual with tuberous sclerosis and severe infantile polycystic kidney disease has a deletion affecting both genes.

GENETIC COUNSELLING

About two thirds of cases are new mutations. Genetic counselling to affected parents is straightforward as non-penetrance is a rare event[35] so their offspring have a 50:50 risk of being affected and affected individuals have a 60–70% risk of seizures and a 50% risk of learning difficulty. Counselling apparently normal parents about the risk of a second affected child is more difficult. Accurate counselling can only be given after full clinical examination of both parents, including ultraviolet light examination of the skin in a darkened room and direct fundoscopy through dilated pupils. Although rarely helpful, cranial computed tomography and renal ultrasound should also be offered as a positive finding significantly alters the risk assessment. Single renal cysts are ignored but polycystic disease or angiomyolipoma are significant. Echocardiography for genetic counselling is unreliable[36] and skeletal survey is unhelpful,[37] but echocardiography is helpful in screening the at risk newborn. Siblings of an affected isolated case should be offered the same screening as their parents because it is known that parents have a 2% recurrence risk even if they have been previously screened. Antenatal diagnosis is now possible for very large affected kindreds who show clear linkage to chromosome 16 but not for other families. Gene deletions are difficult to detect but where detected offer more reliable diagnosis than linkage: at present this remains a research technique. With the exception of very large families, those families who link to the TSC1 gene on chromosome 9 or who are too small for linkage analysis will have to wait for further progress in the isolation of the gene before DNA techniques will help them.

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Use of registers in child health

The role of registers in the planning and provision of health care for children and in health services research has been much debated over the last 20 years. Recently, in the UK, the debate has focused on the resource implications of maintaining registers,[1] on concerns about confidentiality,[2] and on organisational changes in the NHS which appear to threaten the infrastructure of many regionally based information systems, including registers.[3]

It is timely, therefore, to consider the aims and objectives of registers, the extent to which these are fulfilled, and to respond to the challenge that some of these objectives could be met in other ways. From these considerations, I hope the essential and unique characteristics of registers will emerge together with some of the problems of setting them up and maintaining them.

Definition of a register

A register is a list of children with a particular predefined attribute. This attribute is usually a disease or condition