RECENT ADVANCES

Advances in the understanding of tuberous sclerosis

Finbar J O’Callaghan, John P Osborne

Medical textbooks still define tuberous sclerosis (TSC) as a triad of clinical features, mental retardation, epilepsy and “adenoma sebaceum”, first described by Vogt in 1908.1,2 Not surprisingly therefore many clinicians still do not realise that half of TSC sufferers will have normal intellect, a quarter will not have epilepsy, and almost any organ in the body can be affected. Recent advances in molecular genetics and imaging have begun to unravel the complexity of the disease, explaining the mechanisms behind the clinical features and providing insights into how these patients should be managed.

Genetic heterogeneity of TSC
Gunther and Penrose described the autosomal dominant pattern of inheritance of TSC in 1935.3 We now know that there are two genes (and probably only two) causing the TSC clinical phenotype. TSC1 is found on the long arm of chromosome 9, and its protein product is called hamartin.4 The TSC2 gene’s protein product is named tuberin and it is situated on the short arm of chromosome 16, only 48 base pairs of DNA from the gene for adult onset polycystic kidney disease (PKD1).4 This genetic heterogeneity in TSC raises the question of whether the clinical syndrome produced by the two different genes is the same. In some conditions, neurofibromatosis for example, genetic heterogeneity helps explain clinically distinct forms of the disease. However, all the complications of TSC have been seen in both TSC1 and TSC2 except for the contiguous gene deletion syndrome (see below). There may, however, be subtle differences in the phenotype produced by the two genes or by specific mutations. There is already some evidence from case series that mutations in TSC2 tend to produce more severe disease than TSC, but this needs to be confirmed in larger less biased studies.5 We may then see no significant differences in the phenotypes because hamartin and tuberin are thought to function as part of, or at adjacent steps within, the same intracellular pathway.6

Function of the genes
We know that both tuberous sclerosis genes are tumour suppressor genes. Their function is to help regulate cell growth and differentiation. When altered, by mutation, control of cell growth is disturbed and tumours form throughout the body. The strongest evidence for the tumour suppressor hypothesis was provided in 1994 when it was reported that some of the hamartomas of tuberous sclerosis patients showed loss of heterozygosity, either in the chromosomal region 9q34 or in 16p13.7 Markers on 9q34 or 16p13 that were heterozygous in the patient were homozygous in the tumour. The loss of heterozygosity implies that an individual with tuberous sclerosis inherits or acquires through an early embryonic mutation, a deletion in one copy of the gene but only develops lesions when there is a somatic mutation in the other previously normal copy. This two hit mechanism was first proposed by Knudson to explain the pathogenesis of retinoblastoma.10

The tumour suppressor hypothesis is further strengthened both by recent research in the Eker rat (an animal model of tuberous sclerosis), and by studies of the possible intracellular function of tuberin. The Eker rat, which has a mutation in the rat homologue of the TSC2 gene, suffers from dominantly inherited renal cell carcinoma and subependymal and subcortical hamartomata. Reintroduction of a wild type TSC2 gene suppresses the development of renal tumours in this model.11 A search for sequence homologies at the protein level has revealed a region of similarity between tuberin and the GTPase activating protein GAP3.12 The GTPases are known to be involved in the regulation of cell proliferation and differentiation and it is thought that tuberin may have a role in mediating this activity.

Contiguous gene deletions in TSC
Renal cysts are common in TSC. They occur in a substantial minority of patients and have been associated with both TSC1 and TSC2 disease. A particularly severe phenotype has been observed in some patients (very early onset polycystic kidney disease). This is caused by a contiguous deletion that affects both TSC2 and PKD1 genes.13 It is sensible to perform renal ultrasonography on all newly diagnosed children with TSC to identify this rare problem early. An alternative is to monitor blood pressure and serum creatinine.

Mosaicism in TSC
Some of the patients with contiguous deletions of the TSC2 and PKD1 genes have a milder
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investigation) having further a for two apparently una
tuberous sclerosis and we quote a risk of 2–3%
ected children: this situation does occur in
gonad (gonodal mosaicism) then a phenotypi-
disease in mosaics is variable but can be severe.
If the abnormal cell line is confined to the
gonad then a phenotypically normal parent has a high risk of producing
affected children: this situation does occur in
tuberous sclerosis and we quote a risk of 2–3%
for two apparently unaffected parents (after full
isvestigation) having further affected offspring
after the birth of one child with TSC.

Cranial imaging and TSC
The advent of magnetic resonance imaging
(MRI) has allowed clinicians to image many of
the lesions of TSC with greater clarity. MRI
also has the advantage of not exposing the
indifferent to x rays. Theoretically radiation
could cause a “second hit” in the second copy
of the gene. Cerebral tubers are shown on T2
weighted images but may be more easily visualised on a fluid attenuated inversion
recovery sequence (FLAIR).
The number of
is related to degree of learning difficulty
but variation in the relationship does not allow
prediction for the individual.
Approximately 5% of patients. They arise in the
lateral ventricles close to the Foramen of Mon-
oroe (or rarely in the fourth ventricle), giving
rise to signs and symptoms of raised intracra-
ainal pressure. Untreated this will cause hydro-
cephalus, blindness, and ultimately death.
No feature of a giant cell astrocytoma on imaging
could be caused by renal bleeding. Problematic
giant cell astrocytomas declare themselves
because they give rise to raised intracranial
pressure. In a patient with normal intellect this
easily picked up as they usually present with
classical signs and symptoms. Diagnosis in the
patient with learning difficulty requires more
care as they may not be able to communicate
their symptoms to the carer or clinician.

in TSC
There are common hamartomas that can
develop potenially life threatening conse-
quences. In the kidney, renal angiomyolipomas
are common in affected individuals but infre-
cently cause serious problems (haemorrhage
into renal substance, collecting system, or
retroperitoneally). They are usually easily seen
as hyperechoic lesions on renal ultrasound, but
CT is required to confirm the fat content of any
hypoechoic lesions which might otherwise be a
renal cell carcinoma (a very rare but serious
complication of TSC: such a lesion must be
shown to be HMB 45 negative on biopsy before
nephrectomy is performed or an angiomyol-
ipoma may inadvertently be removed).
The brain, the giant cell astrocytomata occur in
approximately 5% of patients. They arise in the
lateral ventricles close to the Foramen of Mon-
oroe (or rarely in the fourth ventricle), giving
rise to signs and symptoms of raised intracra-
ainal pressure. Untreated this will cause hydro-
cephalus, blindness, and ultimately death.
No feature of a giant cell astrocytoma on imaging
has yet been shown to differentiate it reliably
from a subependymal nodule—it is obstruction of
CSF flow which causes symptoms and which
must be treated.

Diagnosis of TSC
Mutational analysis is expensive and many
mutations cannot yet be detected as it is usual
for mutations to be unique to each family or
individual. For prenatal diagnosis of off
affected individuals, it is now possible to
request this. But for diagnosis, clinical skill is
still often required. The old method of minor
and major criteria is more logically replaced by
examining and investigating for hamartomas.

Table 1 Lesions which are individually rare

| Lesion                          |
|------|-----------------|
| Facial angiofibromas or forehead plaque |
| Periungual fibromas               |
| Shagreen patch                     |
| Retinal hamartoma                  |
| Cortical hamartoma                 |
| Subependymal nodule                |
| Giant cell astrocytoma             |
| Cardiac rhabdomyoma                |
| Renal angiomyolipoma or pulmonary lymphangiofibromatosis |

When two of these lesions are found in one individual, the diag-
nosis of TSC is beyond reasonable doubt. In most affected indi-
niduals it is possible to find evidence of two such lesions.
organs in the same individual without an inherited or early embryonic mutation. In practice, it is usually easy to find two hamartomas in affected individuals. For this purpose, angiomylipomas and pulmonary lymphangiomatosis have to be considered dependent hamartomas as these two lesions often occur together in the absence of other proof of TSC (see table 1). To exclude the disease in an individual, a full clinical examination including fundoscopy and cranial imaging must be undertaken: renal imaging probably confuses this purpose. Echocardiography is only helpful as often as it helps and is not recommended for this purpose. Echocardiography is only helpful in young children. Other features, such as hypomelanic patches, should be taken as an indication for further investigation and not as a reliable sign of TSC. Non-penetration is no longer thought to occur.24

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3 Gnathar M, Penrose LS. The genetics of epilepsy. J Genet 1935;31:413-30.
19 O’Callaghan FJK, Renowden S, Needham C, et al. Renal angiomyolipomas and pulmonary lymphangiomyomatosis have to be considered dependent hamartomas as these two lesions often occur together in the absence of other proof of TSC. To exclude the disease in an individual, a full clinical examination including fundoscopy and cranial imaging must be undertaken: renal imaging probably confuses this purpose. Echocardiography is only helpful in young children. Other features, such as hypomelanic patches, should be taken as an indication for further investigation and not as a reliable sign of TSC. Non-penetration is no longer thought to occur.24

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