New research in tuberous sclerosis

Probably more common than was thought—with more adult complications

Tuberous sclerosis is a serious dominantly inherited condition best known for its presentation during childhood with fits and mental retardation. Articles on the disease have doubled over the past 10 years and have focused largely on improved diagnostic criteria and clinical features, disease prevalence, and genetics. Cranial magnetic resonance imaging is beginning to throw light on the contribution of cerebral tubers to neurological outcome, and complications of the disease in adults are gaining greater importance as both survival and ascertainment improve.

The diagnostic criteria first suggested by Gomez in 1979 have evolved. Facial angiofibromas, ungual fibromas, retinal phakomas, multiple cortical tubers, subependymal glial nodules, and bilateral renal angiomyolipomas are considered pathognomonic. The condition can be diagnosed in an individual with an affected first degree relative if any of the following are found: a shagreen patch, a forehead fibrous plaque, multiple cardiac rhabdomyomas (on histological examination or, in a young child, on echocardiography), a giant cell astrocytoma, an isolated retinal phakoma, or an isolated cortical tuber (on histological examination, computed tomography, or magnetic resonance imaging). Without a family history these lesions are highly suggestive but not diagnostic and further investigations are required. This is also true for the following lesions whether or not there is a family history and at least two should be present to make the diagnosis: polycystic kidneys, typical hypomelanic macules, an isolated renal angiomyolipoma or cardiac rhabdomyoma, pulmonary lymphangiomyomatosis, and multiple cortical or subcortical hypomyelinated lesions. Several other features also suggest the possibility of tuberous sclerosis: seizures, gingival fibromas, molluscum fibrosum pendulum in a child or young adult, rectal hamartomatous polyps, hepatic angio-myolipomas, and renal cysts.

The incidence of tuberous sclerosis at birth is unknown. Recent epidemiological studies report a prevalence of 1 in 12 000 to 1 in 15 000 in children aged under 10 years, but mildly affected cases are rarely diagnosed in childhood so there is a selection bias towards those with mental retardation. Thus the real frequency of mental retardation may be lower than previously thought; a recent study in an unbiased population of patients with tuberous sclerosis showed a prevalence of 38% (95% confidence interval 19% to 56%). This suggests that the true incidence at birth may be as high as 1 in 6000.

In 1987 Fryer et al reported significant linkage with the ABO blood group, suggesting a locus for the tuberous sclerosis gene at chromosome 9q34. This finding was not initially confirmed, and the chance discovery of an infant with an unbalanced 11/22 translocation was followed by linkage in American families at 11q22–q23. A collaborative study combining all available data has confirmed genetic heterogeneity and refined the position of the chromosome 9 locus to within two megabases. There is weaker evidence for a second gene on chromosome 11, and since several pedigrees are negative for both loci a third and possibly more loci may exist. Except perhaps in very large informative families, antenatal diagnosis will not be achieved by closely linked markers but must await the discovery of the gene itself.

About two thirds of cases are new mutations, so a common clinical problem is counselling apparently normal parents about the risk of a second affected child. The risk is 2-5%. The most important assessment is clinical examination, including examination of the skin with a Woods lamp in a darkened room and direct funduscopy through dilated pupils. Cranial imaging is unlikely to cause confusion, and as lesions of tuberous sclerosis have been seen in patients who are clinically normal this should be offered. If renal ultrasonography is used it should be remembered that single renal cysts are common in the normal population but do occur in tuberous sclerosis. Angiomyolipomas would always be suggestive. A blind controlled study of echocardiography for genetic counselling found that this was unreliable. Likewise, a skeletal survey is unhelpful.

Cranial magnetic resonance imaging has proved more sensitive than computed tomography at detecting cerebral tubers, although the relation between findings on magnetic resonance imaging and clinical outcome is not clear cut. The number of tubers is unlikely to predict outcome: most children with more than 10 tubers will be severely retarded, but a quarter of those with less than five are severely retarded and in a series of patients with normal intellects one child had none. Tuber size and location may be more important. The number of large tubers seems to correlate with the number of electroencephalographic foci, and lesions in the occipital lobe correlate best with interictal electroencephalographic abnormalities. The combination of posterior (occipital and temporal) tubers with bifrontal parasagittal tubers and marked bilateral synchrony on an electroencephalogram seems to signal a particularly poor prognosis.

For many, however, the outlook is not so poor. Although patients with tuberous sclerosis do not have an average life span, they live longer than was once thought. An analysis of 40 deaths showed 11 from renal disease and 10 from brain solutions. Unless he adopts completely the London Commission’s ideas and analysis Tomlinson is unlikely to be as radical, and ministers might well be tempted by a smaller investment of political will. The danger is that anything less might not be enough.
tumours—all in children aged over 10 years. Two children died of cardiovascular lesions, and four patients died of pulmonary lymphangiomyomatosis, all of whom were aged over 40. The remaining deaths were from status epilepticus. The implication of these findings is that clinicians need to be more aware of the adult complications of tuberous sclerosis, since in its milder forms the condition seems to be more widespread than was once thought.

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Over the counter treatment for candidiasis

An opportunity to educate

Antifungal creams for external treatment of candidiasis have been available without prescription for some time. This summer sees the launch of over the counter intravaginal treatments by two pharmaceutical companies, and more are likely to follow soon. These will cost about £2 more than the current prescription charge, but many patients may consider this a small price to pay for the convenience and control it gives them.

Vulvovaginal candidiasis is a common problem, frequently discussed in women’s magazines, although the information given is often inaccurate and unscientific. Many women already treat themselves: some apply antifungal cream intravaginally on the end of a tampon, but more often they use other topical treatments—such as yoghurt, garlic, vinegar, Dettol, or TCP. Some even follow “yeast free” diets purporting to “eliminate candida from the body.” Literature advocating these diets ascribes fluid retention, endometriosis, period pain and cramps, and impaired libido to “chronic candida infection.” Clearly patients want to control their own management, and there is a need for wider availability of effective treatments.

These treatments are marketed only for uncomplicated candidiasis occurring in women who have already suffered from, and are able to recognise, the condition; any patient with symptoms for the first time is advised to see her doctor. (As an advertisement in the United States for a similar product suggests, “If you THINK you have thrush, go to your doctor; if you KNOW you have thrush, buy Brand X.”) As manufacturers are keen to gain the support of doctors and pharmacists, the packet inserts contain general advice about candidiasis and warn the patient to consult her doctor if she has symptoms suggestive of a sexually transmitted disease such as vulval blisters, abdominal pain, or an offensive discharge. Other contraindications listed include pregnancy, irregular or abnormal vaginal bleeding, dysuria, pyrexia, vomiting, and diarrhoea.

When over the counter treatment for candidiasis becomes available doctors may see fewer cases overall but more patients presenting with “treatment failure” or recurrent symptoms. Treatment failure will occur if medication is used inappropriately, usually because the initial diagnosis is wrong. Conditions such as bacterial vaginosis may mimic candidiasis, as may sexually transmitted diseases. Trichomoniasis, genital herpes, and genital warts cause vulval soreness and itching, and their management includes a search for concomitant sexually transmitted diseases and notification of sexual partner(s). As sexually transmitted diseases are often asymptomatic all women at risk should ideally attend a clinic for sexually transmitted diseases for full investigation.

The differential diagnosis of recurrent candidiasis includes mild attacks of genital herpes and psychosocial sexual problems. Such problems may also be caused by candidiasis, with painful sexual intercourse leading to tension, which persists after the candida has been eradicated. These patients will have most pronounced symptoms during sexual intercourse and may have vaginismus on examination.

Proved recurrent candidiasis needs investigation for an underlying cause, although one is seldom found. Recognised predisposing factors include diabetes, immunosuppressant drugs, and HIV infection. Despite popular belief there is no convincing evidence that modern oral contraceptives increase the risk of vulvovaginal candidiasis. As doctors we should aim to educate our patients, encouraging self treatment when appropriate, but we should remember that in more complex cases a full sexual history must be taken and the patient examined.

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