Non-penetrance in tuberous sclerosis

David W Webb, John P Osborne

Abstract

Non-penetrance has not been reported in tuberous sclerosis when modern non-invasive investigations have been performed. We report a four generation family in which there was a subject with minimal expression and another with non-penetrance between a great grandfather and his great grandson. This situation highlights the need for full investigation of children of tuberous sclerosis patients before counselling a low recurrence risk for the disease.

The skipped generation is a well recognised feature of autosomal dominant conditions and should imply non-penetrance. It can only be considered to have occurred when the non-penetrant subject has both an affected parent and an affected child: in addition the non-penetrant subject must have been rigorously investigated to exclude minimal features of the phenotype.

Using modern standards of investigation skipped generations have not been reported in tuberous sclerosis. However, minimal expression of the phenotype is a well recognised feature of the disease. We report a family who have been thoroughly investigated and have a subject with minimal expression and another with non-penetrance between a great grandfather and his great grandson.

Case report

A 40 year old man had a father and two sibs with tuberous sclerosis. He was examined for a genetic linkage study clinically and with ultraviolet light and direct fundoscopy and, in addition, had a cranial CT scan, renal ultrasound, and x ray skeletal survey. All investigations proved normal. His three children were also examined clinically and with Woods light and direct fundoscopy and because of negative findings

were counselled as having a negligible recurrence risk for the disease.

Two years later his daughter's first child suffered his first fit lasting 35 minutes, eight days after a measles, mumps, and rubella immunisation at 13 months of age. On examination the boy had several hypomelanotic macules typical of tuberous sclerosis. He also had a retinal phakoma and on cranial CT scan there were multiple calcified periventricular nodules. He has suffered no fits since but his development, which was previously normal, is now retarded. His great grandfather has facial angiofibromas, hypomelanotic macules, and ungual fibromas. The child's grandfather was re-examined clinically, with ultraviolet light, and by direct and indirect fundoscopy. He was found to have a single fleshy ungual fibroma (fig 1) on the little toe of his left foot. This had not been there when he was first seen or when he had last cut his toe nails. No other signs were found. A cardiac ultrasound showed two probable rhabdomyomata in the right ventricular wall and right ventricular out-flow tract (fig 2). Cranial magnetic resonance imaging was normal.

The child's mother was also re-examined clinically and with ultraviolet light, direct and indirect fundoscopy, cranial CT scan, renal ultrasound, echocardi-

Figure 1 A fleshy ungual fibroma (arrowed).

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Figure 2 A probable cardiac rhabdomyoma protruding from the right ventricular wall (arrowed).

Figure 3 A cerebral magnetic resonance image with possible non-calcified subependymal nodules (arrows).

graphy, and cranial magnetic resonance imaging. The only significant finding has been three possible non-calcified subependymal nodules visible on T1 weighted magnetic resonance imaging and not on computerised tomography (fig 3).

Discussion

Non-penetrance is clearly a rare occurrence in tuberous sclerosis. There is one previously reported case of affected first cousins whose parents were probable obligate carriers and who were found to be normal on clinical examination and who had normal cranial CT scans.¹ Renal ultrasound, echocardiography, and cranial magnetic resonance imaging were not performed. Rushton and Shaywitz² reported a three generation family with an affected uncle and nephew. The obligate gene carrier was clinically normal but not investigated. Because of the protean

manifestations of this disease, true non-penetrance can only now be considered to have occurred when modern techniques have been used to exclude the diagnosis in patients at risk. Two other previous reports are not adequate for this reason.^{3 4}

Our case of minimal expression, the grandfather, was associated with the late appearance of an ungual fibroma and led to an inaccurate estimate of the risk of recurrence. Before being counselled this man was rigorously investigated in a manner felt to be appropriate at the time. It has recently been suggested that echocardiography may be a useful screening procedure^{5 6} and this would have been helpful if it had been performed at an earlier date. The finding of multiple cardiac echodensities in a patient with a 50% risk for tuberous sclerosis would be sufficient to suggest, but not prove, the diagnosis. Echocardiography is likely to be most helpful in childhood as the lesions are more easily and more frequently seen than in adults. Sonographic-pathological correlations have not been established for the echodense lesions described in adults with the disease and for this reason we remain cautious about the interpretation of such lesions.

This man's daughter is as close as we have seen to representing true non-penetrance for this disease. She may in time develop cutaneous features of the disease, too late to be of help for her own genetic counselling. While calcified subependymal nodules are a primary diagnostic feature, the finding of uncalcified nodules which are apparent only on cranial magnetic resonance imaging and not on cranial CT scanning is not diagnostic. They may represent heterotopic grey matter and the scans have been thought by more than one neuroradiologist to be normal.

This family has been previously reported as a three generation family with no history of fits or mental retardation⁷ (the great grandfather is III.1). They highlight the problem of how to investigate children of tuberous sclerosis patients before counselling a

negligible recurrence risk for the disease in future generations. Where a family member has a 50% prior risk for the disease rigorous investigation would seem reasonable, particularly as non-penetrance is so rare. Cranial CT scans should be performed. We have previously argued that renal ultrasound should not be included as part of a routine protocol to screen parents of an apparent sporadic case.⁸ It may be helpful if done early in life as isolated angiomyolipomata have not been reported in childhood in the absence of tuberous sclerosis. Single cysts which can cause problems of interpretation in adults are rare in childhood. Multiple renal cysts are more likely to represent tuberous sclerosis.

The situation of a second affected child born to clinically normal parents is a different problem and has been reported several times in tuberous sclerosis.⁹⁻¹¹ This might occur because of variable disease expression or true non-penetrance, but also because of non-paternity or germinal mosaicism. Despite all investigations it will therefore still be necessary to counsel a small recurrence risk to the parents of a sporadically affected child.

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