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Reduced penetrance in tuberous sclerosis

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SUMMARY Two first cousins are reported with clinical evidence of tuberous sclerosis. The intervening brother and sister show no evidence of the disease on clinical and Wood's lamp examination, nor on CT scan.

Genetic counselling in tuberous sclerosis is usually without difficulty. The condition behaves as a Mendelian dominant, is variable in expression, and is highly but not fully penetrant. Somewhere between a half and two-thirds of cases are fresh mutations and the rest are inherited from an affected parent. If a thorough ophthalmic and dermatological examination is carried out and this is combined with a brain scan (CT) to look for intracranial calcification, the overwhelming majority of gene carriers can be identified. We present a family in which two first cousins have tuberous sclerosis. The two intervening parents have no evidence of being gene carriers after careful clinical examination and CT scanning.

Case reports

Patient II.1 (fig 1) was born after a normal term delivery. No neonatal problems were encountered but at 6 months he began to have infantile spasms. Clinical examination revealed no abnormal physical signs. A skull *x*-ray was normal but the EEG showed multifocal discharges. He was given 40 units of ACTH daily for 10 days and the injections were then tailed off. At 3 years of age he developed adenoma sebaceum on his face and at this stage was also noted to have hypomelanotic areas on his trunk. His IQ was estimated to be 61. A further skull *x*-ray was taken when he was 5 years old and a number of calcified nodules typical of tuberous sclerosis were seen adjacent to the ventricles. By the age of 7½ years the facial lesions had progressed to the extent that he needed cosmetic surgery (fig 2). The histology of the lesions removed at surgery was compatible with that found in adenoma sebaceum.

Patient II.2 (fig 1) was born after a normal term delivery. Her early development seemed normal and at the age of 8 years she was walking and talking. She then began to regress at school and it was observed that she was having frequent 'blank spells'. An air encephalogram was performed at this stage but unfortunately the patient had a cardiac arrest during the procedure and suffered a severe neurological insult. The picture taken showed paraventricular calcification.

On examination at the age of 15 years the patient had no speech and was bedridden. She was profoundly spastic with increased tone in all four limbs.

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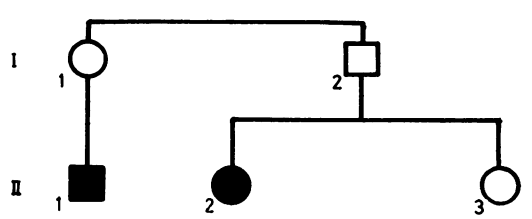

FIG 1 *Family pedigree.*

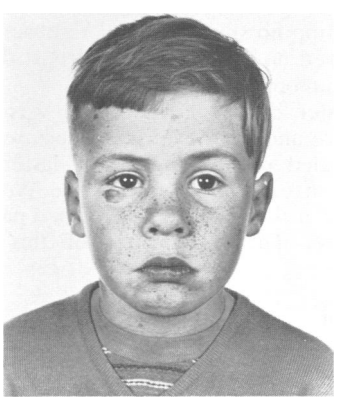

FIG 2 *II.1. Note the early signs of adenoma sebaceum.*

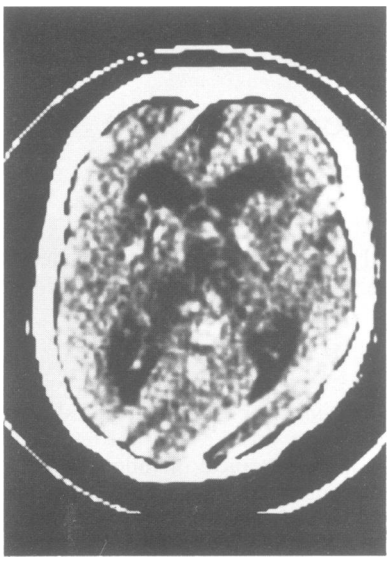

FIG 3 *II.2. Note the periventricular calcification.*

Her reflexes were brisk and she had extensor plantar responses. She could recognise her family but needed considerable care. On examination of her skin no lesions were seen on her face or on her trunk. A Wood's lamp examination was not possible but a CT scan showed typical lesions of tuberous sclerosis (fig 3).

The mother of patient II.1 (I.1, fig 1) is aged 65. She is of normal intelligence and has had no seizures. Examination with the Wood's lamp was entirely normal and CT scan showed no intracranial pathology. No retinal phakomata were seen.

The father of patient II.2 (I.2, fig 1) was 69 when seen. He had no significant past medical history and in particular was of normal intelligence and had never had a seizure. On examination with the Wood's lamp no skin lesions were observed. A CT scan showed no evidence of tuberous sclerosis. No retinal phakomata were seen.

The sister of II.2 (II.3, fig 1) was of normal intelligence and had never had a seizure. Examination revealed no suspicious skin lesions and this included an examination using the Wood's lamp. Her CT scan showed a single calcified paraventricular nodule. The significance of this finding is uncertain.

Discussion

There have been few reports of obligate gene carriers for tuberous sclerosis who on dermatological examination and CT scan have had no evidence of the disease. Wilson and Carter[1] reported, briefly, a brother and sister with tuberous sclerosis whose parents had no evidence of the disease, and the examination included CT scan. Other reports of reduced penetrance do not fulfil all the criteria needed to ascertain minimal manifestation. Rushton and Shaywitz[2] presented a three generation family with tuberous sclerosis in which two heterozygotes were asymptomatic and had a normal dermatological examination including further scrutiny using a Wood's lamp, but no brain scans were obtained. The parents of the sibs reported by Lowry *et al*[3] had normal skin and skull *x*-rays but CT scans were not performed.

The family in the present report provides further evidence that a normal skin examination and a brain scan can very occasionally mislead. It is of course possible that two fresh mutations occurred, but this is unlikely. With the advent of CT scanning it has become easier to confirm the diagnosis of tuberous sclerosis in childhood in those in whom other evidence of the disease is difficult to interpret. In general, when there are no skin lesions in adult life there is little evidence to support that the scan will show characteristic intracranial pathology. However, an exception occurred in one of our patients (II.2) where there were no skin lesions, but clear evidence of tuberous sclerosis was visible on the CT scan.

This family also highlights the difficulty in the interpretation of single calcified nodules on the CT scan. We are still uncertain about the significance of this finding, and we could not definitely exclude the possibility that patient II.3 was an asymptomatic carrier of tuberous sclerosis.

Similar problems may arise in otherwise healthy first degree relatives who have a single hypopigmented macule. The importance of hypopigmented macules in the general population is unknown. In a newborn survey[4] 35 macules were found in a survey of 4641 infants. Follow up was only possible in six and in all cases the lesions disappeared. There is also uncertainty about whether histological features can definitely distinguish a macule of tuberous sclerosis from other lesions.

The existence of these families with reduced penetrance makes the exclusion of the carrier status in first degree relatives problematical. However, the number of reported families with reduced penetrance remains very small and, in general, potential gene carriers with normal CT scan and skin examination can still be reassured, albeit, never totally cleared.

References

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