

Short Report

Natural history of a fibrous cephalic plaque and sustained eight decade follow-up in an 80 year old with tuberous sclerosis complex type 2.

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ABSTRACT

Introduction: Fibrous cephalic plaques (FCP) are a characteristic manifestation of tuberous sclerosis complex (TSC) and occur in one third of cases. Their natural history and long term course is unknown, as is the outcome of long term follow-up of TSC cases in old age.

Phenotype and methods: We describe an 80 year old with TSC due to a c.2784dupC TSC2 mutation, who was diagnosed in infancy with an FCP and was regularly followed up at the TSC clinic over 8 decades with regular epilepsy treatment and renal monitoring.

Results: Regular clinical photography and clinical records document the plaque at different ages. The FCP naturally resolved at 74 years. Facial angiofibromas also faded with time in the last decade. His epilepsy and renal abnormalities remained under control with careful surveillance and monitoring.

Discussion: Natural aging in the eighth decade causes progressive laxity of collagen and leads to natural resolution of FCPs. This novel finding with a unique 80 year follow up yields valuable insights into the aging changes within FCPs and facial angiofibromas as the pathways linking facial angiofibromas and FCP's through the TGF- β 1 pathway are now being elucidated.

Conclusion: We present a clinical odyssey showing the natural progression and history of FCPs in TSC and comment on the mechanistic pathways allowing potential interventions in this disfiguring condition. TSC cases can be successfully managed and complications – particularly in the brain and kidney, can be avoided over an entire lifetime. This is encouraging for long term prospects for patients with TSC.

INTRODUCTION

Fibrous cephalic plaques (FCP; also known as forehead plaques) are a characteristic manifestation of tuberous sclerosis complex (TSC).^{1,2} They occur in around a third of cases, often in childhood, and vary in size and position.³ Their natural history is unknown, as often they are removed in early life, either surgically or by laser treatments, for cosmetic reasons. Histopathological examination shows that they are composed of bundles of reticular collagen with decreased elastic fibres, and are histologically similar to skin angiofibromas and fibrofolliculomas. We describe the clinical course of a large FCP in a patient with TSC2 over an 80 year period. Reports of long term follow-up of TSC cases over several decades are unknown and potential complications – particularly in the brain and kidney, can be avoided over an entire lifetime. Survival for more than 80 years is encouraging for long term prospects for patients with TSC.

PATIENT PHENOTYPE

The patient, aged 80 years on most recent examination in 2018, had an onset of tonic-clonic seizures at eleven months old, following earlier appearance in infancy of a large cephalic plaque (Figure 1). He had subsequently regular clinical follow-up at 1-2 yearly intervals since 1955. On examination at 18 years, he had multiple large facial angiofibromas, an FCP in the right temporo-parietal area, measuring ~90mm on its longest axis, multiple

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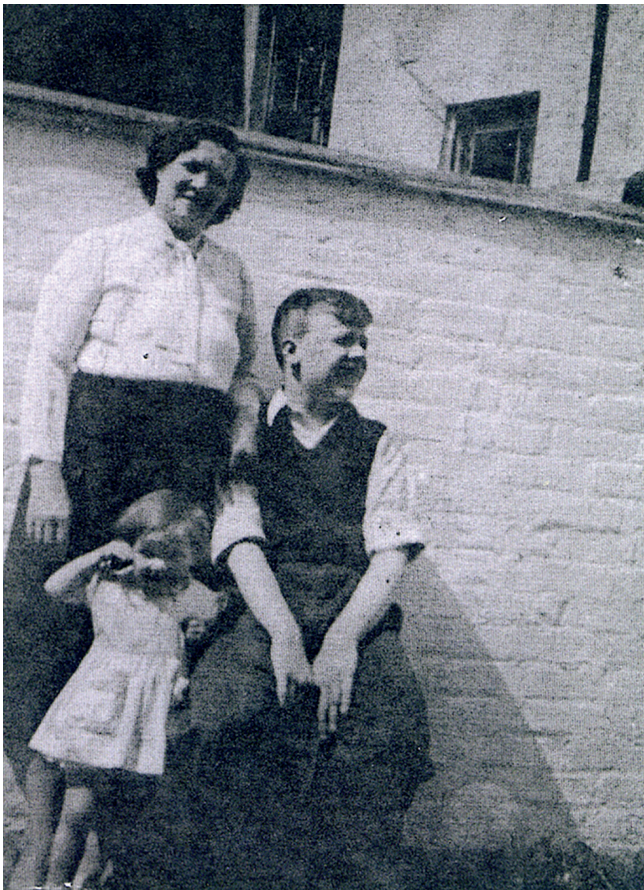


Fig 1. The patient aged 15 with his mother and younger sister, showing the large FCP in the right temporal region.

hypopigmented macules on his trunk and some groin skin tags. He had severe learning difficulties, no speech and had limited understanding and the ability to perform some simple commands. He also had well controlled epilepsy. Examination at 41 years noted the cephalic plaque on the right temple measuring 92x90mm (from scale photographs) on its longest axis, and multiple facial angiofibromas (Figure 2a,b). He was kept indoors in residential accommodation as he disliked the outdoors. Regular ultrasound of his renal tracts to monitor angiomyolipoma formation confirmed slow growing angiomyolipomas bilaterally (40mm diameter largest



Fig 2. Frontal and right lateral views of the patient aged 41 showing severe angiofibromas (2a) and the FCP (2b).

lesion at age 70 and 79mm at age 80). Regular computed tomography of brain to monitor development of cortical tubers and potential sub-ependymal giant cell astrocytoma and other intracranial complications, showed some only periventricular calcification but at the last scan attempt, at age 75, he was too agitated and no further scans were attempted with the agreement of his family. Genetic testing confirmed a c.2784dupC mutation within the TSC2 gene. At 80 years he was having 1-2 partial seizures per week, controlled with Levetiracetam (Keppra), and clonazepam, and his angiofibromas had lessened in intensity, redness and size (Figure 3a) compared to age 41. His cephalic plaque had a residual diameter of 88x87mm with a small ridge remaining at the frontal border and the majority of the plaque area is now confluent with the scalp skin (Figure 3b). The shrinkage of the plaque commenced around seven years ago and has now resolved entirely leaving a small anterior ridge. Parental testing was not possible as both parents were deceased but had no evidence of any features of tuberous sclerosis on examination in late life, and recent mutation testing of other siblings has been normal so this may be a de novo mutation.



Fig 3. Frontolateral and right lateral views of the patient aged 80 showing less vascularization of the angiofibromas (3a) and resolution of the FCP (3b).

DISCUSSION.

FCPs are a characteristic feature of TSC and form part of the 2012 diagnostic criteria. ⁴ Their natural history is unknown as terminology has changed over the decades and most cases where the lesions are large (>50mm diameter on the longest axis) are now generally treated by early surgical removal, vascular laser therapy or laser CO₂ ablation. Recently, topical sirolimus preparations have shown some effect on shrinkage. ⁵ Some plaques may previously have been described in the literature descriptions of skin lesions in TS as shagreen patches – collagenomas or connective tissue nevi which tend to occur predominantly on the lower back. ⁶ FCPs are more common in patients with TSC2 mutations, and may be more likely to occur on the left side of the body, as are some other TSC-related skin lesions. Our patient had a TSC2 mutation and right-sided FCP, with more intense angiofibromas on the right side, along with some large right nasal angiofibromas. Some evidence suggests that cilium laterality genes in mice

may account for a left-sided preference. ⁷ The histological features of FCPs are similar to skin angiofibromas and folliculomas. Angiofibromas are another common feature in TSC. Fibrofolliculomas are a common presentation in Birt-Hogg-Dubé syndrome, but have only rarely been described in TSC - both tend to cluster more commonly in the peri-nasal area. ⁸ Our patient has been followed up at clinics from 18 years of age giving a rare clinical odyssey visible over eight decades. ⁹ The resolution of the forehead plaque suggests that there is a finite lifespan for these lesions and natural collagen decay as part of the aging process may have hastened resorption of the collagen naturally. There is some evidence that sun exposure worsens lesions in TSC, including the facial angiofibromas. Sun protection advice is now routine, with sunscreen applied to sun exposed areas, particularly the peri-nasal region of the face – an area which may get more sun exposure. Our patient had difficult behaviour (he lay down and just refused to get up) when taken outside, so was generally kept indoors. This may have contributed to the improvement in his FCP and his angiofibromas, as he had less exposure to UV radiation over time, compared with the normal population.

The natural history of the FCP suggests that interventions that induce collagen decay, such as radiation therapies or other skin treatments, may be a beneficial adjunct in these disagreeable lesions. The use of mTOR inhibitors may increasingly help management of these lesions and may alter their natural history. Therapeutic steroid use, including triamcinolone acetonide, has recently been shown to improve collagenomas and may act by reducing transforming growth factor β 1 (TGF- β 1) in fibroblasts and increasing basic fibroblast growth factor (bFGF), which may inhibit fibroblast mitosis and collagen synthesis. ¹⁰ Research into the early clinical use of these treatment modalities and therapeutic targets in combination might help future management of patients with these displeasing lesions. Patients who decline to have the FCP's removed surgically either because they are not aware or bothered by the lesions or would be unco-operative because of behavioural difficulties, can be reassured that they are generally self-limiting over time. Until recently there has been a high mortality rate in cases of TSC – particularly in cases with learning disability. Regular renal ultrasound showed non-progressive cysts and very small angiomyolipomas and cranial imaging showed no progression of his periventricular calcification and no complications due to any intracranial tumours. This case shows that increasingly TSC patients can live a normal lifespan and using the latest consensus guidelines on surveillance and management ¹¹, careful regular monitoring of the brain (particularly for sub-ependymal giant cell astrocytomas) and renal tracts (particularly for angiomyolipomas) and management of learning difficulties can allow achievement of a normal lifespan with regular but minimal monitoring to avoid complications. ¹² His epilepsy was manageable and occasionally newer therapeutic options became available and were tried effectively, however he continues to have weekly seizures. Evidence shows that careful early treatment of epilepsy is a major factor in the

diminishment of seizures with age and in the prevention of learning difficulties. Wei *et al* ¹³ have shown that if the first AED is effective, then patients may outgrow their seizures with age. In our patient, early onset of the epilepsy in an era when therapeutic options were very limited has probably not allowed optimum efficacious treatment of the seizures (compared to today's treatments) with resultant persistence of his learning difficulties. With refractory seizures associated with cognitive disability ¹¹, this is something we hope will become less common with strong adherence to more modern guidelines.

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