

Case Report

Misdiagnosis of tuberous sclerosis in a Nigerian girl: A case report and review of literature

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Abstract

Tuberous sclerosis is a rare neuro-cutaneous syndrome, one of the phakomatosis, characterized by facial angiofibromas (adenoma sebaceum), mental retardation and epilepsy. This classic triad occurs in less than one half of patients, probably in one-third, thus requiring a high index of suspicion to diagnose. Consequently it may easily be misdiagnosed as neurofibromatosis or other medical conditions. This is a case report of tuberous sclerosis in a 13-year-old Nigerian girl that was misdiagnosed as neurofibromatosis because of her cutaneous lesions. This paper discussed the case and reviewed the literature. A comprehensive medical clerkship, thorough physical examination, high index of clinical suspicion and neuroimaging investigations are required to confirm diagnosis.

Keywords: Facial angiofibroma, Nigerian, tuberous sclerosis, shagreen patch

Résumé

Bourneville est un syndrome neuro-cutané rare, de la phakomatosis, caractérisée par l'angiofibromas du visage (adénome sebaceum), retard mental et l'épilepsie. Ce classique triade se produit au moins de la moitié des patients, probablement à un tiers, nécessitant ainsi un indice élevé de suspicion à diagnostiquer. Par conséquent, il peut facilement être arrive comme Neurofibromatose ou d'autres conditions médicales. Il s'agit d'un rapport de cas de Bourneville dans une fille de moins de 13 ans qui était arrive comme Neurofibromatose en raison de ses lésions cutanées. Ce document discuté du cas et revue de la littérature. Un stage médicale complète, d'un examen approfondi de la physique, index haute de suspicion clinique et enquêtes neuroimaging sont tenus de confirmer le diagnostic.

Mots-clés: Angiofibroma du visage, du Nigéria, tubéreuses sclérose, patch shagreen

Introduction

Tuberous sclerosis is an autosomal dominant disorder classified as a phakomatosis and characterized by glial cell tumors, which arise in the cerebral hemispheres and retina. It is clinically characterized by the triad of epilepsy, mental retardation and adenoma sebaceum.^[1] The frequency of tuberous sclerosis has been estimated to be 1 in 10 000, about a third as common as neurofibromatosis. It is rivaled only by neurofibromatosis, among all the phakomatoses, in its plethora of radiologic, pathologic and clinical manifestations.^[2] The nodular eruptions (neuromas) of neurofibromatosis may be commonly mistaken for the cutaneous

lesions (especially the facial angiofibroma) of tuberous sclerosis by non-specialist practitioners. Manifestations of tuberous sclerosis can become obvious at any age, but most patients have clinical symptoms before they are aged 10 years. The classic triad of the disease occurs in less than one half of patients, probably in one-third^[3], thus requiring a high index of suspicion to diagnose.

The availability of neuro-imaging facilities like computerized tomographic (CT) scan and magnetic resonance imaging (MRI) has made it possible to demonstrate the presence of cortical hamartomas, white matter abnormalities and subependymal nodules in the brain. The CT findings are

characteristic, though MRI is the imaging of choice as the cortical tubers can be seen in 95% of patients.^[3] We present the case of a 13-year-old primary school girl who was misdiagnosed as a case of neurofibromatosis because of her skin lesions.

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A 13-year-old primary school pupil who presented to a private general practitioner (GP) with multiple, non-pruritic facial papulo-nodular eruptions. She had no fever, facial swelling or insect bites but had had several attacks of afebrile seizures prior to presentation. The GP referred the patient to the Dermatology clinic of the University Teaching hospital with a tentative diagnosis of neurofibromatosis. The patient was evaluated at the Dermatology clinic by a medical registrar who also made a diagnosis of neurofibromatosis but referred to the Neurology clinic for further evaluation of the recurrent afebrile seizures which he could not explain.

Clinical evaluation in the neurology clinic confirmed the presence of facial eruptions, which has been there from age 3 years, and has been gradually increasing in number and size. The afebrile seizures were of generalized tonic-clonic type, with onset at 5 years. The father noticed poor academic ability and slowness in response to questions (psychomotor retardation). The pregnancy, labor and delivery were uneventful. The developmental milestones were normal. Family history revealed no relevant information. General examination revealed a young girl with a weight of 32 kg and a height of 1.28 m, without pallor, jaundice, peripheral fluid retention or lymph node enlargement. She has multiple papulo-nodular eruptions of varying sizes over the malar, frontal scalp and nasal bridge [Figure 1]. In addition, she has hypo-pigmented patches over the upper back [Figure 2] and a toughened elevated patch over the lower back – ‘shagreen patch’ [Figure 3]. The examinations of her respiratory, cardiovascular and abdominal systems were unremarkable.

Neurologically, she had an intact sensorium with no speech abnormality. She was unable to perform simple arithmetic sums. There was no evidence of cranial nerve palsies. The motor and sensory evaluation revealed no abnormality. There were no cerebellar features, primitive reflexes or signs of meningeal irritation. Neuropsychological evaluation, using the Raven standard progressive matrix (a culture-free text) and the Slosson’s drawing coordination test, demonstrated sub-normal intelligence. Simple reaction time test showed significant psychomotor retardation. A clinical diagnosis of tuberous sclerosis based on



Figure 1: Picture of the patient showing the ‘adenoma sebaceum’ (facial angiofibromas)



Figure 2: Picture showing the hypomelanotic patch on the upper back



Figure 3: Picture of the shagreen patch in the patient

the presence of facial angio-fibromas, epilepsy and mental retardation was entertained.

She had a computerized tomographic (CT) scan of the brain, which revealed multiple calcified

periventricular nodules [Figures 4a and b]. There was no shift of the midline structures and the ventricles appear normal. Renal ultrasonography, plain chest X-ray, echocardiography and CT scan of the orbits were normal. She was given sodium valproate tablets 200 mg t.i.d. with significant reduction in seizure frequency. She was eventually lost to follow-up after a year of treatment with anti-epileptic drug.

Discussion

The diagnosis of neuro-cutaneous syndromes (phakomatosis) constitutes a challenge to medical practitioners in the tropics because of the rarity of the diseases and the plethora of clinical features that characterized them. Following the report of the first African child with tuberous sclerosis in 1967,^[4] there have been other reported cases from Nigeria,^[5,6] Togo,^[7] Guinea,^[8] Tunisia,^[9] Algeria^[10] and Kenya.^[11] A detail medical clerkship, thorough clinical examination and high index of clinical suspicion are required to make the diagnosis in most cases, especially if and when the components of the syndrome are incomplete.

Tuberous sclerosis is a congenital disease of hereditary type in which the abnormal gene has been localized to one of two sites, the long arm of chromosome 9 (9q³⁴), designated as TSC 1 (encoding hamartin) and the short arm of chromosome 16 (16p^{13.3}) designated as TSC 2 (encoding tuberin).^[12-15] The former site is linked closely to the ABO blood group genes.^[14] The mutations are at loci of tumor-suppressor genes that are inactivated and this may, in part, explain the proclivity to develop various growths and hamartomas.^[16-20] It is determined by a single autosomal dominant gene, in about 20% of cases with an estimated prevalence of 1 : 50 000 to

1 : 300 000. The remaining cases (as many as 80%) are attributed to a spontaneous gene mutation, the frequency of which is calculated to be 1 : 20 000 to 1 : 50 000.^[1,19]

The disease involves many organs in addition to the skin and brain, and it may assume a diversity of forms, the least severe of which is difficult to diagnose.^[12] The clinical diagnosis is virtually certain if the triad of seizures, mental retardation and adenoma sebaceum is present.^[3] It is the early stage of disease and the *forme fruste* (least severe form) that proves difficult to diagnose, and here the experienced dermatologist can be of great help. It is important to note that epilepsy and delay in psychomotor development are by no means diagnostic of tuberous sclerosis, since they occur in many diseases. It is in these cases and also in every sizable population of people with epilepsy or mental retardation, especially when the family history is unrevealing, that a search for the dermal equivalents of the disease (the hypomelanotic ash-leaf spots, adenoma sebaceum, collagenous patch, phakoma of the retina or subungual or gingival fibromas) is so rewarding. The finding of anyone of these lesions provides confirmation of the partial and atypical case.^[12]

Seizures occur in most patients as is the case in our patient.^[12] Some children present with 'infantile spasms', but the spectrum of the seizure disorder ranges from focal seizures to tonic-clonic seizures, sometimes progressing to status epilepticus. Seizures are seen in all mentally deficient patients, and in approximately 70% of patients with normal mental status.^[2,21,22] Mental impairment or retardation can be observed in 40–82% of patients, and in almost all patients with seizures, the seizures begin before the patient is aged 2 years.^[2,22,23] The mental deficiency may be relatively stable or it may be progressive. It

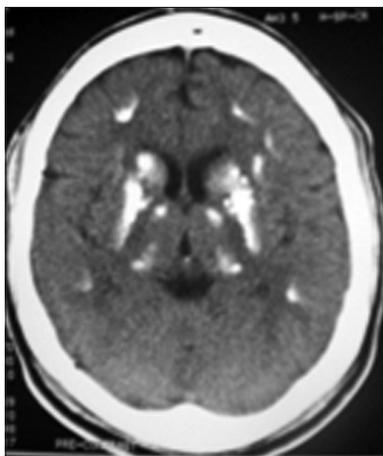


Figure 4a: Pre-contrast CT scan of the brain showing the paraventricular calcified lesions

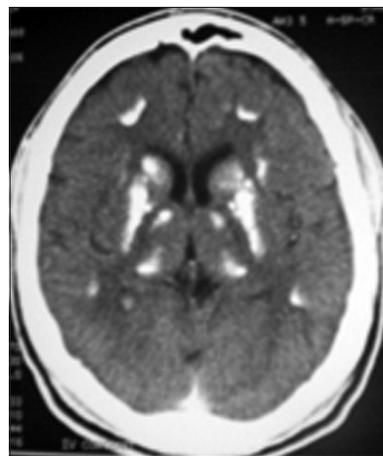


Figure 4b: IV contrast CT scan of the brain showing the periventricular hyperdense lesions

accounts for about 0.66% of the mentally retarded in institutions and 0.32% of patients with epilepsy.^[2,23] The medical literatures contain reports of patients with no mental disturbance and have never had convulsions.^[21,22,24] It is possible that data drawn from mental hospital population have exaggerated the overall frequency of mental retardation due to tuberous sclerosis, as up to 33% of patients have normal intelligence.^[2] Neurologic signs are considered uncommon, except when an intracranial neoplasm develops.^[23] Our patient had no evidence of focal neurological deficit though the CT brain scan revealed cerebral nodules and periventricular hamartomas. Retinoscopy may reveal an oval, white plaque (glial hamartoma) in the peripheral fundus. It is from this lesion, called a phakoma that van der Hoeve (1920) derived the term that is applied to all neurocutaneous disorders of this class. They may be bilateral in 80% of cases.^[25] Drusen of the optic nerve head may also be seen.^[25] Cutaneous manifestations are also a major aspect of this disorder^[14] as evident from this case. The earliest lesions are hypopigmented spots over the trunk and limbs; these are present in 83% of cases and are seen most clearly under ultraviolet (UV) light (Wood's lamp). Adenoma sebaceum, present in 40 to 80% of cases, manifests around the fifth year of life as a pale, pink, slightly raised rash. It consists of discrete, elevated, 0.1 to 1.0 cm spots that fade on pressure; they appear first in the nasolabial folds, spreading over the face in a 'butterfly' pattern over the cheeks and forehead, sparing the upper lip. During the teenage years, the lesions tend to coalesce and darken in color to a brown or deep red. Subungual fibromas and a 'shagreen patch' may be identified in older children. The shagreen patch, present in 30 to 70% of cases, is seen as thick, toughened, yellowish skin over the lower back.^[13,26,27]

It is important to note that Birt-Hogg-Dubé (BHD) syndrome, a dominantly inherited predisposition for development of fibrofolliculomas, trichodiscomas and acrochordon,^[28] and multiple endocrine neoplasia1 (MEN1) may manifest with facial angiofibromas.

CT and MRI of the brain are the most sensitive screening imaging studies.^[29] Currently, MRI is considered the modality of choice for the evaluation of the brain in patients with diagnosed or suspected tuberous sclerosis, but it is less sensitive than CT in the identification of calcifications of the brain.^[30,31] Most hamartomas lie adjacent to the cerebrospinal fluid (CSF) pathway, predominantly along the lateral ventricular surface. They usually manifest as partially calcified subependymal nodules, most frequently along the thalamostriate sulcus, an area rich in germinal cells during

embryogenesis.^[29,30] Noncalcified hamartomas may be difficult to demonstrate with CT.^[31] Similar subependymal and intracerebral calcifications may also occur as a result of gestational inflammatory conditions such as toxoplasmosis or cytomegalic inclusion disease, but the inflammatory process generally produces other cerebral abnormalities such as hydrocephalus, microcephaly or areas of encephalomalacia. Cortical atrophy with secondary ventricular dilatation is often present in tuberous sclerosis.^[32] Contrast enhancement of subcortical or subependymal nodules, usually occurring in those closest to the foramen of Monro, is said to indicate malignant degeneration. Obstructive hydrocephalus due to an underlying giant cell astrocytoma may be seen in about 10% of patients.^[3,33]

The first, and most specific, finding with MRI is multiple subependymal nodules. As one might expect, the presence of calcification in these nodules may not be visualized using standard spin-echo imaging. This, however, does not appear to decrease the ability to diagnose tuberous sclerosis correctly on MRI. Marked T1 and T2 prolongation within a subependymal nodule suggests malignant transformation. The second characteristic finding, dilated ventricles, is said to be seen in 50% of patients.^[29,31] A third characteristic MRI finding reported in the McMurdo study was the presence of multiple cortical and subcortical foci of increased signal intensity on the T2-weighted images. These most likely represent the cortical tubers, presumably the cause of the seizures or mental retardation, or both, and are the most sensitive finding on MRI, being present in all patients.^[29]

CT is the modality of choice for evaluating renal lesions because of its ability to delineate cystic lesions and lipid-containing angiomyolipomas^[34-36] but the prohibitive cost of CT in developing countries like Nigeria makes renal ultrasonography an acceptable, sensitive and readily available option. Renal angiomyolipomas, which may present with flank pain or hematuria, occur in 50–90% of patients but only rarely contain enough adipose tissue to be observed on plain radiographs.^[34] Severe renal involvement may result in renal failure in patients aged 10–30 years. Hypertension may develop as a result of renal disease.^[37] Findings on excretory urograms or retrograde pyelograms can vary widely, depending on the number and size of cysts or angiomyolipomas, including bilateral renal enlargement or distortion of the collecting systems caused by cysts or angiomyolipomas.^[34,36] Hamartomatous polyps can be present in the colon.^[38] Gastric polyposis also can occur; this can be depicted on barium studies.^[39]

Most findings detectable on plain radiographs are musculoskeletal or thoracic. One half of the patients with tuberous sclerosis have musculoskeletal lesions. Changes include osteoporosis and cystic defects in the metacarpals, metatarsals and/or phalanges. Erosions of the tufts of the distal phalanges, the result of unguis angiofibromas, may be observed.^[40] A periosteal reaction is observed in tubular bone; some authors characterize this reaction as having an undulating appearance. Heterogeneous sclerosis can affect the entire axial skeleton. Multiple bone islands with an apparent natural propensity for the diploic space may be observed. Macroductyly and expansile-enhanced bone density that is restricted to a single rib are described.^[41] Plain skull films often reveal sclerosis or widening of the diploic space, which is related to the administration of phenytoin.

Chest radiographs rarely can depict evidence of interstitial fibrosis or honeycombing.^[35] Occasionally, the appearance of the chest is compatible with its appearance in lymphangioleiomyomatosis (LAM).^[42] The connection between tuberous sclerosis and LAM is unclear. Pneumothorax is an infrequent complication in interstitial fibrosis and LAM. Approximately one-fourth of patients can have cardiac rhabdomyomas,^[43] which places these patients at risk for congestive heart failure. Specificity with respect to plain radiographic findings in patients with tuberous sclerosis is problematic because many of these lesions occur in other conditions; however, conventional radiographic findings often support the diagnosis of tuberous sclerosis.

Nuclear medicine studies may have a minor role in the assessment of this condition. In patients who have intractable seizures, epileptogenic foci may originate from a single tuber. Single photon emission CT imaging of the brain is useful during the ictal phase of seizures to detect the hyperperfusion of a seizure focus; this information can be valuable because surgery can be an option.^[44] Renal scintigraphy demonstrates multiple hypoperfused and hypofunctioning lesions, such as cysts or angiomyolipomas, of the kidneys; however, these findings are nonspecific.^[34,36]

Angiography is dominant in the characterization of vascular derangements associated with tuberous sclerosis. Some authors believe that progressive degenerative changes or compromise of the media results in aneurysms.^[45] Thoracic and abdominal aneurysms can develop in patients as young as 10 years or younger. Intracranial aneurysms also can be present, and one source proposes that these should be included as a non-primary diagnostic feature of tuberous sclerosis.^[45] Generally, angiography is not necessary to evaluate the kidney. However,

if performed, angiography may demonstrate hypervascularity, neovascularity and small arterial aneurysms in the angiomyolipomas. Cystic lesions are avascular. Findings believed to be suggestive of angiomyolipomas include pseudoaneurysms and a lack of arteriovenous (AV) shunting. Percutaneous embolization may be helpful in controlling intratumoral hemorrhage from renal angiomyolipomas, especially if multiple lesions are present; in this situation, surgery may be difficult or impossible to perform.^[46]

The usual life span of patients with tuberous sclerosis varies. Infants with cardiac rhabdomyomas in whom a severe prenatal arrhythmia or respiratory distress develops may require surgical excision of the tumor on the first day of life.^[43] Many mildly affected patients survive until their 50s or 60s. Standard anticonvulsant therapy usually suppresses the seizure tendency,^[46] but corticosteroids (ACTH or prednisolone) may be needed for treatment of infantile spasms in affected children.^[47] Ventricular shunting and surgical removal of cerebral neoplasms that may be causing increased intracranial pressure or recalcitrant epilepsy have been helpful.^[48] The expert panel on tuberous sclerosis consensus conference recommended CT or MRI scanning every 1–3 years for children and every 5–7 years or as clinically indicated in adults to facilitate early detection and complete excision of cerebral tumors.^[49] Periodic surveillance program in children and adults with tuberous sclerosis without renal lesions include 1–3 years regular renal ultrasonography but more frequently (every 6–12 months) for those with renal abnormalities.^[49,50]

The management of affected patients is often multidisciplinary involving the neurosurgeon, neurologist, nephrologist, pulmonologist, cardiologist, ophthalmologist and the genetic counselor among others. Several drugs have been tried in the management of cerebral hamartomas, renal angiomyolipomas, pulmonary LAM and disfiguring angiofibromas in TS. These include atorvastatin, doxycycline, sorafenib, cytokine interferon-gamma (IFN-g) and rapamycin.^[51]

The antibiotic, doxycycline, is a matrix metalloproteinase (MMP) inhibitor that has been shown in a case report to reduce MMP levels in urine from a LAM patient. Furthermore, reduction in urine MMP levels in that case correlated with improvement of pulmonary function.^[52] In a recent study, atorvastatin was found to inhibit the proliferation of fibroblasts while also inhibiting constitutive phosphorylation of mTOR, S6 kinase and S6 in *animal models with tuberous sclerosis genes*.^[53] The cytokine interferon-gamma (IFN-g) is another

candidate therapeutic agent for the treatment of tuberous sclerosis complex because the presence of a high-expressing IFN- γ allele has been linked to significantly reduced kidney tumor burdens in *animal models*.^[54] Sorafenib (also known as BAY 43-9006 and Nexavar[™]) is an oral multi-targeted kinase inhibitor thus possessing inhibitory effects on angiogenic and tumorigenic molecular targets and may be useful for treating TSC-related tumors.^[55] While rapamycin effectively reduces the size of many TSC-associated tumors in humans, tumor regression does not occur in all cases and tumor regrowth is generally observed with the cessation of treatment.^[56-58] Furthermore, survival data in a TSC preclinical model suggests that the combination of rapamycin plus sorafenib, a multi-targeted kinase inhibitor that targets the VEGF pathway, may be more effective than single agent rapamycin.^[51]

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