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lesson of the month (1)

Tuberous sclerosis presenting with confusion and agitation

This lesson describes a case of tuberous sclerosis presenting with confusion and agitation. The condition is briefly reviewed and learning points are emphasised for clinicians encountering similar presentations.

Lesson

A 59-year-old lady with a background of moderate-to-severe learning difficulties and epilepsy was admitted with confusion and agitation. Her medication consisted of diazepam 10 mg TDS and phenytoin 100 mg TDS. On inspection she had an erythematous nasolabial rash. Examination of her cardiovascular, respiratory and abdominal systems was unremarkable. Of note in her neurological examination were absent knee-jerk reflexes.

Her blood tests were fairly unremarkable with the only abnormalities being a mildly elevated alkaline phosphatase (ALP) of 122 (32–120 u/l) and an elevated phenytoin level at 25 (10–20 mg/l). Her chest and abdominal radiographs were normal. A previous computed tomography (CT) head scan from a year ago was reviewed and revealed small vessel disease suggesting vascular dementia.

A review from the psychiatrists suggested that her acute-on-chronic confusional state was probably due to vascular dementia; with phenytoin toxicity being suggested as a differential diagnosis. Her phenytoin dosing was optimised, and her confusional state was managed with diazepam and quetiapine. The patient improved gradually and was discharged home.

Unfortunately, the patient was readmitted the next day with right-sided facial twitching and periorbital bruising. Her bloods revealed no new abnormalities. A urine dipstick and culture were positive for a urinary tract infection for which antibiotic treatment was commenced. A head CT and orbits were also obtained which revealed multiple calcific densities in the periventricular/subependymal region as well as in the caudothalamic groove; which are in keeping with tuberous sclerosis – a diagnosis that had not previously been made. A subsequent dermatological review of the patient with the diagnosis in mind revealed other features of tuberous sclerosis (TS), namely adenoma sebaceum and subungual fibromas.

The patient and her family were informed of the diagnosis and the patient is currently obtaining genetic counselling.

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Discussion

TS is a rare, inherited neurocutaneous disorder. It is autosomal dominant with an incidence of approximately one in 5,000–10,000 live births.[1] However, only one third of the cases are familial.[2]

Two distinct genetic loci responsible for TS have been identified: one on chromosome band 9q34 (referred to as TSC1) and another on chromosome band 16p13 (TSC2).[3] The TSC1 gene encodes hamartin and the TSC2 gene encodes the tuberin protein. Normally, the hamartin forms a complex with the tuberin protein, which then acts as a negative regulator of the cell cycle. In the absence of the functional tuberin–hamartin complex, cells spend less time in G1 (resting-phase of the cell cycle) and quiescent cells are induced to enter the cell cycle[4,5] possibly leading to the formation of multiple benign neoplasms of the brain, kidney and skin – the clinical features of TS.

The diagnostic criteria for TS are based upon specific clinical features (Boxes 1 and 2).

Box 1. The major features of tuberous sclerosis.

Location	Sign
Head	Facial angiofibromas
Fingers and toes	Nontraumatic ungula or periungual fibromas
Skin	Hypomelanotic macules
	Shagreen patch
Brain	Cortical tuber
	Subependymal nodule
	Subependymal giant cell astrocytoma
Eyes	Multiple retinal nodular harmartoma
Heart	Cardiac rhabdomyoma
Lungs	Lymphangiomyomatosis
Kidneys	Renal angiomyolipoma

Box 2. The minor features of tuberous sclerosis.

Location	Skin
Teeth	Multiple pits in dental enamel
Rectum	Harmatomatous rectal polyps
Bones	Bone cysts
Brain	Cerebral white-matter migration tracts
Gums	Gingival fibromas
Liver, spleen etc	Non renal hamartoma
Eyes	Retinal achromic patch
Skin	Confetti skin lesions
Kidneys	Multiple renal cysts

The diagnosis of TS requires two major features, or one major feature and two minor features. The more recognised triad of seizures, mental retardation and facial angiofibromas (Vogt's triad) occurs in fewer than 50% of patients with TS.[7]

TS is a rare disease and therefore not in the forefront of the clinician's mind. Also, the awareness of the disease is usually limited to Vogt's triad or to individuals with severe neurological pathology. TS can present at any age with a varying phenotype. Therefore establishing the clinical diagnosis of TS is exceedingly difficult. Consequently, the true prevalence of the disease within the population might be greater than that which is known.

A recent study estimated total population prevalence between about seven and 12 cases per 100,000, with more than half of these being undetected.[8] The total population prevalence figures have steadily increased from 1:150,000 in 1956, to 1:100,000 in 1968, to 1:70,000 in 1971, to 1:34,200 in 1984, to the present figure of 1:12,500 in 1998. One possible explanation for this could be the use of imaging techniques, such as ultrasound, CT and MRI, which have enabled the diagnosis of difficult and also many non-symptomatic cases of TS.

It was imaging that eventually led to this patient's diagnosis and its importance in diagnosing patients with rare genetic disorders needs to be recognised.

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