# Endocrinopathy complicating a case of Tuberous sclerosis

Sir,

Tuberous sclerosis (TSC) is a multi-system genetic disorder affecting skin, brain/nervous system, kidneys, heart, and lung and leading to growth of non-malignant tumors. A combination of symptoms may include seizures, developmental delay, behavioral problems, skin abnormalities, lung and kidney disease. TSC is caused by a mutation of either of two genes, TSC1 and TSC2, which code for the tumor suppressor proteins hamartin and tuberin, respectively.

A 26-year-old female with no premorbidities presented with complaints of galactorrhea for the past 10 days and menstrual irregularities over the past 6 months. Galactorrhea was spontaneous. Her last childbirth 4 years ago was uneventful. She had no headache, vomiting, visual impairment. She denied any history of substance abuse, drug intake (anti-psychotic, anti-emetic, hormonal preparations), hypothyroidism, chronic liver or kidney diseases, epilepsy. There was no significant family history. She was a well-nourished female with mild pallor, tiny nodule on face, subungual fibroma in hands [Figures 1 and 2]. There was spontaneous galactorrhea and mildly tender breasts without any signs of inflammation. Systemic examination was entirely normal with normal IQ. Ophthalmologic evaluation revealed white disk-shaped retinal hamartoma. Routine laboratory investigations including renal and liver function tests, thyroid profile were normal. Serum prolactin was 85 ng/mL with FSH-4.66 and LH-4.21 mIU/ml. In view of the theoretical possibility of involvement of cell groups of other anterior pituitary lineage, tests for evaluation of other anterior pituitary hormones were carried out and were found to be normal. Abdominal and pelvic

ultrasound revealed no abnormality. Chest X-ray showed bilateral interstitial infiltrates [Figure 3]. Echocardiogram of heart was normal. Computed tomography (CT) scan revealed multiple intracerebral calcifications [Figure 4]. These calcified lesions/sub-ependymal hamartomas are seen along the lateral surface of the lateral ventricles giving rise to characteristic candle dripping appearance. Magnetic resonance imaging (MRI) of the brain ruled out the presence of any pituitary mass. The combined clinical scenario along with the radiologic findings leads to the diagnosis of TSC with hyperprolactinemia. Patient was prescribed cabergoline 0.5 mg twice-daily, which resulted in amelioration of galactorrhea and regularization of menses.

Tuberous sclerosis lesions infrequently cause symptoms in the endocrine, gastrointestinal (GI), and lymphatic systems. It is unclear; however, why these organ systems should be less prone to hamartoma formation than the central nervous system, kidneys, or skin. Perhaps the hamartomas at the endocrine, GI, and lymphatic systems, remain small, clinically insignificant, and unrecognized in most cases. There is a growing body of evidence, though anecdotal, that TSC patients develop hormone-secreting tumors involving the neuroendocrine system at higher frequency than the general population. Cushing's disease,[1,2] hypoglycemia secondary to insulinomas,[3-7] precocious puberty,[8,9] thyrotoxicosis,[10] hypercalcemia secondary to parathyroid adenomas,[10-12] hyperprolactinemia,[13] and acromegaly[14] have all been reported in TSC patients. The circulating prolactin of our patient may be of pituitary origin or may possibly be secreted ectopically by a hamartoma. In addition, in at least one TSC patient, multiple endocrine abnormalities have been noted.[10] These and other clinical observations have led to speculation that there is an overlap between TSC and multiple endocrine neoplasia type 1 (MEN type 1). However, the brain, skin, and renal involvement by TSC is quite distinct from anything seen in the MEN syndromes, apart from facial angiofibromas that can be seen in 88% of patients with MEN type 1.[15]

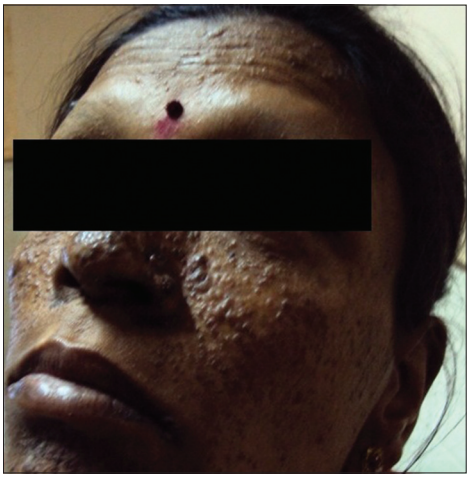

**Figure 1:** Tiny nodules present diffusely over face suggestive of adenoma sebacium

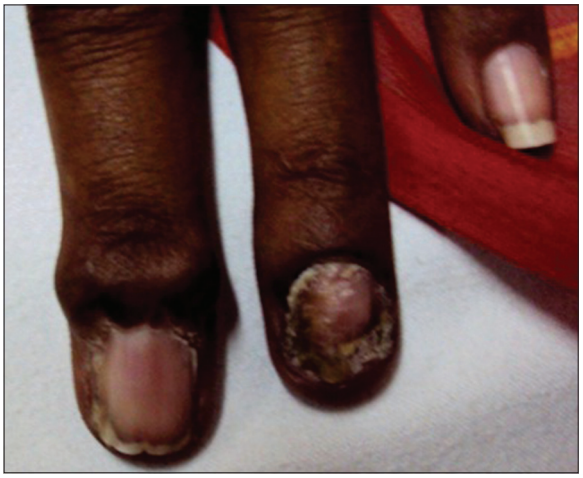

**Figure 2:** Subungual fibromas

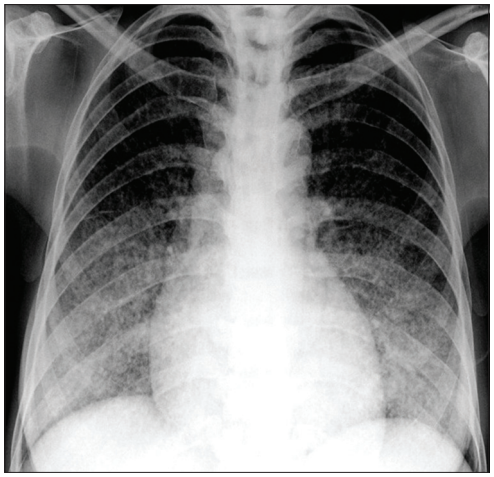

**Figure 3:** Chest X ray PA view showing bilateral interstitial infiltrates

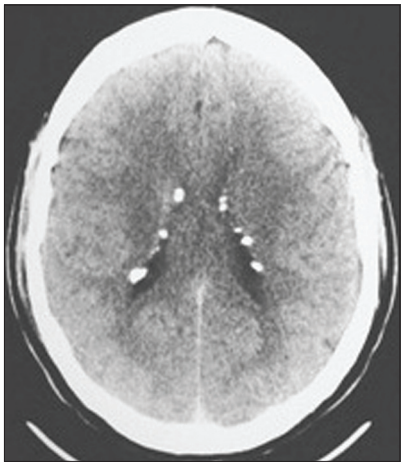

**Figure 4:** CT Brain reveals calcified lesions/ subependymal hamartomas seen along the lateral surface of the lateral ventricles giving rise to characteristic candle dripping appearance

There has been evidence linking neuroendocrine tumors to the AKT/mTOR/S6 kinase pathway that is regulated by the hamartin/tuberin (TSC1/TSC2) complex. Thus, it is beginning to appear that the occurrence of these neuroendocrine tumors (NET) in TSC is more than random coincidence.

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DOI: 10.4103/2230-8210.107883

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