Introduction

Tuberous sclerosis complex (TSC), described by Bourneville (Bourneville’s disease) in 1880, is a rare autosomal dominant neurocutaneous syndrome with almost complete penetrance but variable expressivity. Two loci on chromosomes 9 (TCS 1) and 16 (TCS 2) produce the phenotype, both encoding proteins (hamartin and tuberin, respectively) with tumor suppresser function. When TSC1 and TSC2 not activated, leads to uncontrolled cell cycle progression and the proliferation of hamartomas throughout the body. In about one-third of cases, an affected person inherits an altered TSC1 or TSC2 gene from a parent who has the disorder. The remaining two-thirds of people are born with new (de novo) mutations in the TSC1 or TSC2 gene. These sporadic cases occur in people with no history of tuberous sclerosis complex in their family.

The term epiloia was coined by Sherlock to indicate triad of epilepsy, low intelligence and adenoma sebaceum (Vogt triad). The estimated prevalence is one case per 6000 to 10,000 individuals. TSC is characterized by a variety of hamartomatous lesions in various organs and commonly involve the brain, skin, kidneys and heart. Other organs like lungs, bone, eyes, teeth and gastrointestinal tract can also be affected. Diagnostic criteria were reviewed in 1998 by Roach et al. (Table 1).

Case Report

A 35 year old female presented with 5 months history of constipation and lower abdominal discomfort. She used to pass stool with increased consistency once or twice in a week with feeling of incomplete evacuation. History of prolonged straining and manual evacuation was absent. She used to take laxative however, use of enema was absent. On examination, she had pallor with multiple facial angiofibromas (Figure 1a), forehead fibrous plaque, shagreen patch on trunk (Figure 1b), periangual and ungual fibromas (koenen tumor) in both hands (Figure 1c) suggestive of tuberous sclerosis complex. On abdominal examination she had palpable left renal mass. Detailed history and examination did not reveal seizure, mental retardation and behavioral problems. (J Dig Endosc 2010;1(3):161-4)

Keywords: Tuberous sclerosis complex - Constipation - Colorectal polyps - Renal angiomyolipoma
normal too. Abdominal plain radiograph was unremarkable. Ultrasonography abdomen showed bilateral enlarged kidneys with multiple echogenic lesions in renal parenchyma. Computed tomography (CT) abdomen showed multiple small cysts in both kidney and large predominantly fatty lesions in both perinephric regions arising from kidneys. Fatty lesions showed islands of soft tissue with internal septations and blood vessel suggestive of angiomyolipoma (AML) (Figure 2a and Figure 2b). Colonoscopy showed extrinsic compression on sigmoid colon (scope was easily

<table>
<thead>
<tr>
<th>Major features</th>
<th>Minor features</th>
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<tbody>
<tr>
<td>Facial angiofibromas or forehead plaque</td>
<td>Multiple randomly distributed pits in dental enamel</td>
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<tr>
<td>Nontraumatic ungual or periungual fibroma</td>
<td>Hamartomatous rectal polyps</td>
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<tr>
<td>Hypomelanotic macules &gt; 3</td>
<td>Bone cysts</td>
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<tr>
<td>Shagreen patch (connective tissue nevus)</td>
<td>Cerebral white-matter “migration tracts”</td>
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<tr>
<td>Cortical tuber</td>
<td>Gingival oblomas</td>
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<tr>
<td>Subependymal nodule</td>
<td>Non renal hamartoma</td>
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<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>Retinal achromic patch</td>
</tr>
<tr>
<td>Multiple retinal nodular hamartomas</td>
<td>“Confetti” skin lesions</td>
</tr>
<tr>
<td>Cardiac rhabdomyoma single or multiple</td>
<td>Multiple renal</td>
</tr>
<tr>
<td>Lymphangiomatomatosis</td>
<td></td>
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<tr>
<td>Renal angiomyolipoma</td>
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</table>

Definite TSC. Two major features or one major feature plus two minor features
Probable TSC. One major feature plus one minor feature
Possible TSC. One major feature or two or more minor features

Figure 1a: Photograph showing: multiple facial angiofibromas (Multiple small papules of <5mm diameter symmetrically distributed in the nasolabial folds, cheeks, nose and chin)

Figure 1b: Photograph showing: shagreen or “leather” patch (irregularly shaped plaque of thickened skin, slightly elevated, with a “peau d’orange” surface) on trunk (arrow)

Figure 1c: Photograph showing: koenen tumors (smooth, firm, nodular or fleshy lesions that are adjacent to or underneath the nails) in hand (arrow) with partial disrupt of the nail

Figure 2a: Abdominal CECT scan showing: multiple small cysts (red arrow) in both kidney and large predominantly fatty lesions in both perinephric regions arising from kidneys suggestive of renal angiomyolipoma (yellow arrow)

Figure 2b: Abdominal CECT scan showing: Fatty lesions showed islands of soft tissue with internal septations and blood vessel suggestive of renal angiomyolipoma
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negoatable) and multiple small (< 1cm) benign colorectal polyps (Figure 3). Histopathological examination of rectal polyp revealed elongated crypts lined by tall columnar epithelium with abundant mucin suggestive of hyperplastic polyp. NCCT of brain was normal. Family screening done with skin and retinal examination, brain imaging and abdominal ultrasound did not reveal TSC in family members. Patient refused for molecular genetic testing. As asymptomatic renal angiomyolipoma is a benign condition, patient was treated conservatively with laxatives and prokinetic agents. Patient is under regular follow-up without any further complications.

Figure 3: Sigmoidoscopy showing: benign colonic polyp (H/E showed hyperplastic polyp)

Discussion

In tuberous sclerosis complex gastrointestinal manifestations are uncommon and limited literature is available regarding the same. TSC can involve the entire gastrointestinal tract, mainly by hamartomatous lesions.

The oral manifestations are fibromas, papillomas, hemangiomas and enamel hypoplasia. Fibromas are reported in nasopharynx and esophagus. Hamartomatous and hyperplastic polyps are described in stomach. Most common gastrointestinal manifestation of tuberous sclerosis complex is incidentally detected asymptomatic hamartomatous rectal polyps. Adenomatous and hyperplastic polyps have been reported too. The hamartomatous rectal polyps are included as minor diagnostic criteria of TSC. Evidence of carcinoma-in-situ was found in an elderly patient of rectal polyp. Two cases of invasive colorectal adenocarcinoma are described; one of them was a 17-year-old girl. Leiomyomatosis like lymphangioleiomyomatosis of the ascending, transverse, and descending colon have been described in a female of intractable chronic constipation. The angiomyolipoma of colon and leymoma of colon and jejunum have been reported in the literature. The hepatobiliary lesions, described in patients with TSC are hepatomegaly, angiomylipomas, hamartomas, lipomas, leymoma, adenoma and fibromas. The hepatic angiomylipomas are mostly asymptomatic, but some may present with abdominal pain, general malaise, and lump. Although the pancreas is rarely involved, hypoplasia, hamartoma, mucoviscidosis and tumors including insulinoma, non-functioning islet-cell tumor, gastrinoma and pheochromocytoma have been reported.

The clinical manifestations of gastrointestinal involvement depend on underlying pathology and includes constipation, abdominal discomfort, abdominal pain, abdominal distension and rarely gastrointestinal bleeding. Acute colonic pseudoobstruction (Ogilvie’s syndrome) has been reported in a young male. Intestinal hypoperistalsis was described in a newborn who presented with intestinal pseudoobstruction and cardiac rhabdomyoma. In younger patients of TSC with neurological manifestations, constipation in is not unusual because of the increased risk of hypotonia resulting in weak abdominal wall muscles and difficulties in potty training and toileting. In these patients, long term constipation may cause dilatation of large bowel resulting into further aggravation of constipation. The data regarding constipation in absence of neurological involvement is limited. Constipation in these groups of patients can be because of intestinal structural lesions, intestinal hypomotility, acute colonic pseudo obstruction, or associated hyperparathyroidism due to parathyroid adenoma. Extrinsic compression of colon by large renal tumor can also cause constipation in these patients. Sometimes pathogenesis of constipation may be unexplained. The pathogenesis of intestinal hypomotility in TSC is unknown; however, involvement of connective tissue may be a possible cause. Loss of elastin fibers has been documented in the media of the aorta in patients who presented with aortic aneurysm in tuberous sclerosis complex. Although, we found no obvious explanation for constipation in our case; however, extrinsic compression of sigmoid colon by renal mass and intestinal hypomotility may be contributing factors.

The presentation of our patient was interesting because she presented to the gastroenterologist with symptoms like constipation, abdominal discomfort and abdominal lump; however, the usual clinical features, such as seizure, mental retardation and behavioral problems were absent. TCS mostly presents with neurological (seizures, mental retardation, behavioral problems), dermatological and symptomatic renal manifestations (abdominal pain, nausea, vomiting, awareness of lump, hematuria, anemia, and hypertension). None of these features was present in this patient except dermatological manifestation for which she never visited to

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Management of a patient with TSC requires multidisciplinary approach. Evaluations following initial diagnosis and surveillance recommendations are summarized in Table 2. Treatment should be symptomatic and organ specific. Treatment of constipation includes behavioral modifications and laxatives for long term. Laxatives should be avoided in childhood. Intractable constipation due to structural lesions may require surgery, sometimes even colectomy. Seizures are managed with an anti-convulsant medication. Because of the risk of hemorrhage, it is recommended that those with symptomatic renal AML greater than 3.5 to 4.0 cm be considered for prophylactic renal arterial embolization or renal sparring surgery. Facial angiofibroma can be treated with dermabrasion or laser surgery. Genetic counseling is important. With one affected parent, the recurrence risk is 50%. When both parents appear to be unaffected, the recurrence risk is 1 in 22 after one affected offspring and 1 in 3 after two affected offspring. The absence of clinical feature of TSC in other family members indicates de novo (sporadic) mutations in the TSC1 or TSC2 gene.

In conclusion, gastrointestinal manifestation of TSC are uncommon but can occasionally be life threatening. Such patients should undergo regular gastrointestinal evaluation particularly for early detection of colorectal malignancy.

Table 2: Initial Evaluations and Surveillance

<table>
<thead>
<tr>
<th>Initial evaluations</th>
<th>Surveillance</th>
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<tbody>
<tr>
<td>Medical history, Family history</td>
<td>Cranial CT/MRI every 1 to 3 years for children and adolescents</td>
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<tr>
<td>Physical examination with use of a Woods lamp (UV)</td>
<td>Renal USG every 1 to 3 years in persons with no previously identified renal lesions</td>
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<tr>
<td>Ophthalmologic examination</td>
<td>Semiannual renal USG in individuals with angiomylipoma &lt; 3.5 to 4.0 cm</td>
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<tr>
<td>Cranial CT/MRI, Renal USG, Chest CT (for adult females)</td>
<td>Neurodevelopmental and behavioral evaluations</td>
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References


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