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Tuberous Sclerosis Complex: Perioperative Considerations

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ABSTRACT

Background: Tuberous sclerosis complex (TSC), also known as Bourneville disease, is an inherited, progressive neurocutaneous disorder characterized by the potential for hamartoma formation throughout the body. TSC is an autosomal dominant genetic disorder, but more than two-thirds of cases are sporadic.

Methods: Clinical manifestations and treatment options are discussed. Both surgical and anesthetic perioperative considerations are described in this review.

Results: Routine monitoring is appropriate for minor surgical procedures for patients with TSC who have mild disease manifestations. More extensive monitoring is indicated for major procedures that have the potential for significant blood loss and for patients with more severe pathology. Postoperatively, TSC patients should be admitted for monitoring and treatment after more extensive procedures or if significant organ dysfunction occurs. Postoperative complications, which may be related to either the surgery or the TSC pathology itself, may have origins in many different organs and may include seizures, severe hypertension, and bradyarrhythmias.

Conclusion: TSC is a rare disease with a highly variable clinical presentation and provides a multitude of challenges for the patient, the family, and the healthcare team.

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INTRODUCTION

Tuberous sclerosis complex (TSC), also known as Bourneville disease, is an inherited, progressive neurocutaneous disorder characterized by the potential for hamartoma formation in nearly every organ system, including the brain, eyes, heart, lungs, liver, kidneys, and skin.[1-3] The incidence of TSC is estimated to be 1 case per 6,000-10,000 individuals and its prevalence to be 1 case per 14,000-25,000 individuals.[1,4] TSC affects approximately 1 million individuals worldwide and involves all racial and ethnic groups.[3] The presentation of the disease is highly variable, and the diagnosis is typically made clinically.[1-3] According to one series of patients reported by the Mayo Clinic, more than 90% had skin lesions, approximately 90% had symptoms of cerebral pathology, 70%-90% had renal abnormalities, and about 50% had retinal hamartomas.[2] The classic Vogt triad of facial angiofibromas, mental retardation, and intractable epilepsy occurs in no more than 30%-40% of affected individuals.[3]

GENETICS AND PATHOPHYSIOLOGY

TSC is an autosomal dominant genetic disorder; however, more than two-thirds of cases are sporadic, resulting from new, spontaneous mutations.[1,5] The possibility of germline mosaicism, in which apparently healthy parents have 2 or more children with TSC, should be noted.[6] The disease has almost complete penetrance but highly variable expression.[1]

The disease results from inactivating mutations in either the *TSC1* gene, located on chromosome 9q34, or the *TSC2* gene on chromosome 16p13.3.[7] *TSC1* encodes the protein hamartin, while *TSC2* encodes the protein tuberin.[1-3,5,7,8] These proteins form a complex that triggers the GTPase-activating protein Rheb, which inhibits the mammalian target of rapa-

mycin (mTOR), a highly conserved protein kinase involved in regulating cellular metabolism, differentiation, growth, migration, and protein synthesis.[9] Mutations in either *TSC1* or *TSC2* result in loss of their tumor-suppressor activity and the constitutive activation of mTOR, causing abnormal cellular proliferation and differentiation and the capacity for the production of the hamartomatous lesions of TSC.[1,3] Inactivation of both alleles of *TSC1* or *TSC2*, mainly through loss of heterozygosity, is required for hamartoma development.[2,6]

Individuals who are genotypically identical may have pronounced phenotypic differences. The extent and severity of clinical manifestations vary considerably, even among members of the same family, suggesting minimal correlation between a mutation and its clinical consequence. In general, however, patients with mutations in *TSC2* have a greater severity of symptoms than those with mutations in *TSC1* (more frequent and severe epilepsy, moderate to severe mental retardation, cortical tubers, renal angiomyolipomas, retinal hamartomas, and advanced facial angiofibromas).[1,6] Individuals without evident mutations usually have milder phenotypic expression than those with mutations in either *TSC1* or *TSC2*.[2] Additionally, the *TSC2* gene is located only 48 base pairs of DNA away from the *PKD1* gene; a large deletion that affects both the *TSC2* and *PKD1* genes may result in a subset of patients with both TSC and autosomal dominant polycystic kidney disease.[1,5]

CLINICAL MANIFESTATIONS

Dermatologic Manifestations

The most common dermatologic manifestations are hypomelanotic macules, also known as ash leaf spots or Fitzpatrick patches (Figure). Present in 90%-98% of patients with TSC, these white macules are classically rounded at one end and tapered at the other or polygonal in shape and are enhanced by examination with a Wood lamp. They are the earliest cutaneous lesions, usually presenting at birth or in infancy, and are more common on the trunk and buttocks.[1,2,6] Facial angiofibromas, formerly known as adenoma sebaceum, are present in approximately 75%-80% of patients with TSC. They are hamartomatous nodules of vascular and connective tissue and appear in the second to fifth year of life as red or pink papules symmetrically distributed over the centrofacial areas in a butterfly distribution. The lesions become more prominent with age.[1,2,6]

Shagreen patches are connective tissue nevi with irregular borders and raised, grayish-green or light brown roughened surfaces, generally appearing in the lumbosacral area. They are present in approximately 20%-54% of patients with TSC and are rare during infancy, tending to increase in size and number with age.[1,2,6] Forehead fibrous plaques, variants of angiofibromas, are yellowish-brown or skin-colored elevated plaques of variable size and shape. They appear in approximately 20%-36% of patients with TSC and are common at any age. In some children, however, these lesions develop in the neonatal period, and they may be the first skin lesions of TSC.[1,2,6]

Other skin lesions that may occur in association with the disease include molluscum fibrosum pendulum (skin tags on the neck, axillae, or groin, 22.6%), periungual and ungual fibromas (skin-colored or reddish nodules adjacent to or underneath the nails, 15%-20%), and confetti-like macules (stippled hypo-

Figure. Putting a face on the disease. This patient with tuberous sclerosis complex has moderate mental retardation, astrocytomas, 10 additional benign brain tumors, cortical visual impairment, complex seizures, and kidney lesions. As an infant, she had open heart surgery for the removal of a cardiac rhabdomyoma. She has a tuber of the nasal cavity, numerous ash leaf spots, facial angiofibromas, dental pitting, and shagreen patches. (Figure supplied by and published with permission of Ms. Andrea Grenz.)

pigmentation symmetrically distributed over extremities, 2.8%).[1,2,6]

Neurologic Manifestations

Central nervous system symptoms are the leading cause of morbidity and mortality in patients with TSC.[6] The disease is associated with 4 characteristic neurologic lesions. Glioneuronal hamartomas (the eponymous cortical tubers of TSC) are focal developmental malformations of the cerebral cortex, characterized by the proliferation of glial and neuronal cells and exhibiting loss of the 6-layered structure of the cortex and bizarre-appearing giant cells, dysplastic neurons, and astrocytes.[2,3,7] The lesions are variable in size and number and can be detected by magnetic resonance imaging (MRI) as early as 20-26 weeks of gestation.[2,7] Increasing numbers of glioneuronal hamartomas (or, more specifically, tuber-to-brain proportion) tend to be correlated with more cognitive impairment and difficulty with seizure control.[1,10] Subependymal nodules are hamartomas typically seen in the subependymal wall of the lateral ventricles and may protrude into the ventricular lumen. Together with the cortical tubers, they are present in approximately 90% of children with TSC.[4] These lesions are believed to be asymptomatic, but they may undergo gradual transformation into subependymal giant-cell astrocytomas (SEGAs), most commonly within the first 2 decades of life.[2,7] Histologically indistinguishable from subependymal nodules, SEGAs, which are observed in 5%-15% of patients with TSC, usually occur in the region of the foramen of Monro either unilaterally or bilaterally; growth of these lesions may obstruct cerebrospinal fluid flow through the foramen of Monro and result in acute or subacute hydrocephalus and symptoms of increased intracranial pressure.[3] White matter lesions may be present in 80% of these patients.[4]

Seizures are the most common cause of morbidity in patients with TSC.[3] They are the initial manifestation in 90% of individuals, and the prevalence of epilepsy in TSC is reported to be 66%-93%.[4,11] Seizure onset usually occurs within the first 12 months of life, with 15%-20% of patients presenting with infantile spasms.[1,11] The overall prevalence of infantile spasms is estimated to be 30%-45%, and other seizure types (partial motor seizures and generalized tonic-clonic seizures) are also common.[1,3,4] Earlier onset of seizures, particularly infantile spasms, is associated with a worse prognosis for developmental delays and intractable epilepsy.[3] In one study of 361 patients, epileptiform abnormalities were observed in 78%.[11] Epileptogenesis may be associated with abnormal expression of glutamate and GABA receptors in dysplastic neurons and giant cells of glioneuronal hamartomas, as well as with impaired glutamate transport in astrocytes.[11] Not all tubers are epileptogenic, and not all epileptiform activity has a structural correlation.[11]

TSC has a bimodal distribution with regard to cognitive function. The majority (60%-70%) of patients have a normal or mildly depressed intelligence quotient (IQ) (mean IQ of 93), but these patients may display specific cognitive deficits of memory, attention, or executive skills.[2,3] The remaining 30%-40% of patients have severe mental retardation (mean IQ of 30-40); these patients are more likely to have experienced infantile spasms, poorly controlled seizures, and seizure onset before 1 year of age.[2,3] Autism is highly prevalent in TSC, with an incidence of 16%-50% of patients, and has been associated with early onset of seizures, cortical tubers in the temporal lobes, and *TSC2* mutations.[4,10] Children with cognitive impairment are more likely to have features of autism.[10] Other common comorbidities in children with TSC include learning disabilities (71%) and attention-deficit hyperactivity disorder (28%-62%).[4]

Cardiovascular Manifestations

The characteristic cardiac lesion of TSC is the rhabdomyoma that is present in 40%-60% of patients.[12] Cardiac rhabdomyomas are one of the most common primary pediatric cardiac tumors, and up to 96% of infants with these lesions will ultimately be diagnosed with TSC.[2,12] Isolated cardiac rhabdomyomas appear in 30%-50% of cases, and multiple rhabdomyomas appear in 70% of cases.[12] In a review of the literature, detection of these lesions on routine antenatal sonography was the main initial finding in 26 of 44 fetuses.[5] They appear more frequently within the ventricles and walls than in the septum.[2] Although usually asymptomatic, cardiac rhabdomyomas may cause problems because of their location and size. They may cause inflow or outflow obstruction in the heart if sufficiently large; or, if located in proximity to valves, they may cause murmurs and regurgitation (Figure). This turbulent blood flow can predispose individuals with TSC to thromboembolism formation. If located in proximity to conduction tissue, rhabdomyomas can manifest as dysrhythmias such as ventricular tachycardia, supraventricular tachycardia, and Wolff-Parkinson-White syndrome.[13] The lesions usually develop between 22 and 26 weeks of gestation, potentially leading to ventricular hypertrophy, heart failure, and sudden death; however, cardiac rhabdomyomas tend to regress by 6 years of age.[1,12,13]

Individuals with TSC are also predisposed to arterial aneurysm formation, potentially affecting the aorta as well as the carotid, renal, and intracranial arteries.[1]

Renal Manifestations

Renal complications are either the first or second most common cause of mortality in patients with TSC, depending on the study.[1,2] One longitudinal study demonstrated that up to 80% of children had renal abnormalities at age 10.5 years.[3] Almost invariably, these patients are born with normal kidneys and develop renal proliferative disease as they age.[14] The most common renal lesion is the angiomyolipoma, present in 75%-80% of children >10 years of age.[1] The lesions are composed of abnormal blood vessels, smooth muscle, and adipose tissue.[2] They are also the prototype of the perivascular epithelioid cell tumors, a family of tumors that includes lymphangioleiomyomatosis and exhibits immunoreactivity for both melanocytic and smooth muscle markers.[14] Angiomyolipomas are often bilateral, increasing in number and size with age.[1] The female-to-male ratio is 3-4:1.[1] When tumors reach a diameter greater than 4 cm, the tumors are at risk of spontaneous hemorrhage from micro- and macroaneurysms (25%-50%).[2,3] Enlarging tumors also encroach on normal renal parenchyma, leading to chronic kidney disease and end-stage renal disease.[3]

Renal cystic disease occurs in approximately 45% of patients with TSC and varies from an asymptomatic, microcystic disease to a severe, polycystic phenotype. The most severe disease has an early onset and is associated with a contiguous deletion involving both *TSC2* and *PKD1* genes on chromosome 16.[3] These patients may exhibit significant renal insufficiency as teenagers.[3] Although imaging and gross appearance of kidneys afflicted with this contiguous deletion resemble those seen in autosomal dominant polycystic kidney disease, the microscopic features are unique.[5] Patients with renal cystic disease in TSC classically develop hypertension and the potential for impaired urinary concentration, increasing the risk of volume depletion and renal hemorrhage.[3] Individuals may also present with flank pain or gross hematuria.[1]

Although solid renal lesions in patients with TSC are most often fat-poor angiomyolipomas, they may rarely be oncocytomas or renal cell carcinomas.[3,14] Renal cell carcinoma develops in fewer than 2% of patients with TSC and occurs at an average age between 28 years (25 years younger than the average age of presentation in the general population) and 50 years, depending on the study.[3,14] Oncocytomas are benign tumors that are uncommon in the general population; they seem to occur more frequently in patients with TSC than in the general population.[14]

Pulmonary Manifestations

Lymphangioleiomyomatosis (LAM) is the most common pulmonary manifestation of TSC and the third most common cause of TSC-related mortality.[3] It occurs almost exclusively in female patients of childbearing age and affects 26%-48% of female patients, most of whom are asymptomatic.[3] LAM is characterized by the proliferation of abnormal alveolar smooth muscle-like cells, leading to the formation of thin-walled cysts in the lung parenchyma and cystic structures in the axial lymphatics.[15] The most common symptom is dyspnea (more than 70% of patients), and more than 50% of patients have a history of pneumothorax, often recurrent. Other symptoms may include chylous pleural effusions, cough, chyloptysis, hemoptysis, and chest pain.[2,15] Although the chest radiograph may be useful for diagnosing pneumothorax and pleural effusions, it may be normal even in patients with moderate to severe disease. In patients with more severe disease, the chest radiograph may show bilateral, symmetrical reticulonodular and cystic changes, sometimes in a honeycomb or bullous pattern. High-resolution computed tomography (CT) scan is much more helpful in determining lung changes, and most characteristically seen are well-circumscribed, round, thin-walled cysts ranging from 1 mm to several centimeters in size.[3,15] Multifocal micronodular pneumocyte hyperplasia, which consists of hyperplasia of type 2 pneumocytes, frequently occurs with LAM in patients with TSC and is not known to produce clinical symptoms.[1,16]

LAM can also occur in a sporadic form in women who do not have TSC (resulting from 2 somatic mutations in *TSC2*) in addition to its form as a pulmonary manifestation of TSC (associated with germline mutations of *TSC2*).[2,3] Renal angiomyolipomas are present in 32% of patients with sporadic LAM and in 93% of patients with TSC-related LAM.[2] Based on 4 lines of evidence, LAM is thought to be a metastatic neoplasm whose source in the blood, lymphatic system, and lung may be renal angiomyolipomas and the uterus.[3]

Ophthalmic Manifestations

Retinal hamartomas occur in 40%-50% of patients with TSC at any age.[2] Most lesions are asymptomatic, but they may occasionally cause visual impairment as a result of a large macular lesion.[1] Three types of retinal lesions have been described. The most common is a flat, smooth-surfaced, salmon-colored,

semitransparent lesion. The second most common is an opaque, white, elevated, multinodular, calcified lesion resembling a mulberry. The third most common type is a transitional lesion with features of the other 2.[2] A punched-out, achromic patch on the retina, similar to the hypopigmented macules on the skin, may also be seen.[1,2] Additionally, angiofibromas may develop on the eyelids.[1]

Other Manifestations

Oral manifestations may include dental enamel pitting (48%-100%), gingival fibromas (50%), fibrous hyperplasia, hemangioma, bifid uvula, cleft lip and palate, high-arched palate, macroglossia, thickening of the alveolar bone, and pseudocystic lesions of the mandible.[1,6]

Osseous manifestations are usually asymptomatic and include bone cysts in the phalanges of the hands and feet, sclerotic lesions, and periosteal new bone formation.[1]

Gastrointestinal manifestations commonly include hamartomatous polyps in the gastrointestinal tract, particularly in the rectum, and are usually asymptomatic. Papillomas have also been reported.[1]

Hepatic manifestations may include multiple angiomyolipomas. In 2 ultrasonographic studies of patients with TSC, the proportion of individuals with these lesions was 24% and 16%. They grow more slowly than renal angiomyolipomas.[2]

Endocrine manifestations are rare, but pituitary tumors, parathyroid adenomas and hyperplasia, pancreatic endocrine tumors, a pheochromocytoma, and a carcinoid tumor have been reported in conjunction with TSC.[17]

DIAGNOSIS

The diagnosis of TSC is based upon clinical criteria devised at the Tuberous Sclerosis Complex Consensus Conference in Annapolis, Maryland, in 1998 and described in the Table.[18] A definitive diagnosis is made when 2 major features or 1 major feature plus 2 minor features are present. A probable diagnosis is made when 1 major feature plus 1 minor feature are present. A possible diagnosis is made when either 1 major feature or 2 or more minor features are present.[1,18] Absent from the diagnostic criteria are epilepsy and mental retardation, as these conditions are common in the general population and have numerous causes.[18]

Genetic testing is not required for definitive diagnosis when appropriate clinical criteria are met; however, it may be helpful in specific circumstances. Genetic testing is useful in confirming a diagnosis of TSC when patients are young or when they do not meet all criteria for a definitive diagnosis by clinical examination.[2] For the families of patients affected by sporadic causes of TSC, genetic testing can help exclude the presence of DNA mutations in other family members.[2] Genetic testing is also useful for prenatal and preimplantation diagnosis.[2] The overall mutation detection rate is approximately 85%-90%, so a negative genetic test does not necessarily exclude the presence of the disease.[2]

Table. Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features	Minor Features
Facial angiofibromas or forehead plaque	Multiple randomly distributed pits in dental enamel
Nontraumatic ungual or periungual fibroma	Hamartomatous rectal polyps
Hypomelanotic macules (more than 3)	Bone cysts
Shagreen patch	Cerebral white-matter migration tracts
Cortical tuber	Gingival fibromas
Subependymal nodule	Nonrenal hamartoma
Subependymal giant-cell astrocytoma	Retinal achromic patch
Multiple retinal nodular hamartomas	Confetti-like skin lesions
Cardiac rhabdomyoma, single or multiple	Multiple renal cysts
Lymphangiomyomatosis	
Renal angiomyolipoma	

Table adapted from Roach and Sparagana and published with permission.[18]

TREATMENT AND MANAGEMENT

Electroencephalography (EEG) should be performed at diagnosis or if seizures are suspected and should be repeated as clinically indicated. Cranial MRI should be conducted at diagnosis and repeated every 1-3 years until the patient is approximately 21 years of age, unless symptomatic.[2,16] The treatment of seizures is perhaps the most common and difficult feature of management for patients with TSC. These patients benefit from aggressive antiepileptic treatment, as controlling infantile spasms and partial epilepsy leads to improved development.[3] Vigabatrin, a gamma-aminobutyric acid transaminase inhibitor, is efficacious in treating infantile spasms associated with TSC and is generally considered the drug of choice for this purpose.[3] Despite superior efficacy, however, the drug has demonstrated retinal toxicity potentially resulting in irreversible visual field defects or visual loss with an incidence of 30%-40%.[3,4] Corticotropin (adrenocorticotropic hormone), either as a gel or aqueous solution administered intramuscularly, or a

corticosteroid such as prednisone can be used as second-line agents.[3] Treatment of other types of seizures depends upon seizure classification and other comorbidities in the patient but follows the general principles of epilepsy management. Lamotrigine and felbamate may be useful.[3] Barbiturates and benzodiazepines, as well as other sedating anticonvulsants, have a limited role in management and should generally be avoided.[3] A growing body of evidence suggests that mTOR inhibitors such as everolimus may be beneficial in the management of epilepsy in patients with TSC. A clinical trial of everolimus for SEGAs showed an 86% reduction in seizures in patients with concurrent epilepsy.[3]

Unfortunately, the rate of epilepsy refractory to medical treatment in patients with TSC is 50%-80%.[11] For these patients, a ketogenic diet (or possibly carbohydrate restriction alone) and vagus nerve stimulation can be attempted.[3] Resective surgery is another treatment option that must be considered for intractable epilepsy, as it offers significant benefit in seizure reduction or elimination. Novel techniques in neuroimaging and neurophysiology have increased success in localizing complex, multifocal epileptogenic tubers and foci. These techniques include diffusion-weighted and diffusion-tensor MRI, functional MRI, single-photon emission computerized tomography, fluorodeoxyglucose and alpha-methyl-L-tryptophan positron emission tomography, magnetoencephalography, and high-resolution EEG.[11] Additionally, invasive monitoring with intracranial electrodes has made surgery successful in patients who were previously inoperable because of nonlocalizable epilepsy.[11] A systematic review of the literature indicates surgery has resulted in a seizure-free outcome in 57% of cases and a $>$90% reduction of seizure frequency in 18% of cases.[11] A single cortical tuber, focal EEG abnormalities, and focal seizures are findings associated with better outcomes following resective surgery. Findings associated with worse outcomes and seizure recurrence after surgery include the following: tonic seizures, moderate to severe mental retardation, and older age at the time of resection.[11] Potential complicating factors unique to TSC include bilateral multifocal or generalized epileptiform abnormalities, extratemporal location, and possible appearance of secondary epileptogenic foci after resection of a dominant lesion.[11]

The standard intervention for growing and symptomatic SEGAs is operative resection.[3,4] Achieving a gross total resection is important, as any residual astrocytoma tissue is highly likely to recur. Lesions are typically removed by a transfrontal or midline transcallosal approach.[3] Although most SEGAs can be resected surgically, some display serial regrowth or aggressive behavior, are associated with widespread peritumoral edema, or occur in atypical locations such as the hypothalamus or pineal gland.[3] For TSC patients with symptomatic SEGAs not amenable to surgical resection, treatment with mTOR inhibitors such as rapamycin and everolimus may effectively reduce morbidity. In 1 report, rapamycin produced an average reduction in astrocytoma volume of 65%, and everolimus produced a 55% reduction in tumor volume at 1 year.[3] These pharmacologic agents have also demonstrated activity against renal angiomyolipomas, facial angiofibromas, and pulmonary lymphangioleiomyomatosis.[3,16]

Cognitive and behavioral assessments should be performed at diagnosis and at school entry and repeated as clinically indicated.[2] Depending on patient age, the following assessments are recommended: gross and fine motor skills, social-communication skills, global cognitive ability, receptive and expressive language, attentional-executive skills, visuospatial skills, memory, vocational assessment with knowledge of cognitive strengths and weaknesses, adaptive behavior and daily living skills, social care needs, and vocational advice.[4] Appropriate management is directed by clinical findings and may include early intervention programs, special needs school programs, or referral for other social, scholastic, and vocational support.[4]

The dermatologic lesions of TSC are not associated with significant risk of malignant transformation, but treatment may be considered if deemed necessary or desirable by patients for cosmetic reasons.[4] Facial angiofibromas may be treated with laser therapy, dermal abrasion, or surgical removal. Fibrous plaques, ungual fibromas, and shagreen patches may be treated with laser or surgical therapy.[4,16] Cryotherapy is helpful for skin tags.[4]

Renal ultrasonography should be performed at diagnosis and every 1-3 years to monitor the growth of lesions and possible development of malignancy. CT or MRI might be needed to detect complications of lesions, such as hemorrhage and rupture, or to more accurately assess potential malignant transformations and conspicuous, fat-poor lesions.[2,4] Imaging should be repeated every 6 months to 1 year in the case of documented findings.[4] Blood pressure should be measured because of the prevalence of renin-dependent hypertension in TSC patients, and renal function should be assessed (plasma creatinine, urea, and electrolytes).[4] If a bleeding angiomyolipoma is identified, percutaneous arterial embolization or conservative renal-sparing surgery may be employed. For renal cell carcinoma, complete surgical excision is the therapy of choice.[4] Care should be taken to avoid nephrotoxic agents, including nonsteroidal antiinflam-

matory drugs (NSAIDs) and excessive imaging contrast, as well as urological procedures that remove functioning renal tissue.[3] Patients who progress to end-stage renal disease may require renal transplant.[16]

If the patient is a female of reproductive age, serial spirometry, chest x-ray, and high-resolution noncontrast CT scan are indicated for evaluation of pulmonary structural and functional impairments related to LAM.[4,16] In the case of pneumothorax, pleurodesis can be considered. Bronchodilators may be helpful for controlling symptoms in the 15%-20% of LAM patients with reversible airflow obstruction.[3] Oximetry should be performed routinely, and patients should be vaccinated against influenza and pneumococcus.[3] If disease progression is noted, mTOR inhibitors may be indicated.[16] Lung transplantation is performed for end-stage disease.[3]

Cardiac rhabdomyomas are often visualized antenatally by fetal ultrasonography and generally diminish with age. Electrocardiography is performed at diagnosis and repeated if the patient experiences dysrhythmia or unexplained loss of consciousness.[4] Echocardiography is performed in the case of cardiac symptoms. Both modalities are repeated every 6 months to 1 year in patients with symptoms or previously documented findings.[4] Cardiac surgery may be necessary if rhabdomyomas severely obstruct blood flow in the heart and the patient is symptomatic.[16]

Ophthalmic examination is performed at diagnosis.[2] Most retinal lesions are asymptomatic, but if visual impairment is present, the lesions should be followed serially to rule out retinoblastoma.[16] Treatment for exudative retinal hamartomas includes photodynamic therapy.[2]

ANESTHETIC AND SURGICAL CONSIDERATIONS

Patients with TSC are likely to require anesthesia for diagnostic or therapeutic procedures.[19] Determination of the extent of neurologic, cardiovascular, pulmonary/airway, and renal involvement is essential to the preoperative evaluation.[20] No specific anesthetic techniques or agents are absolutely contraindicated in patients with TSC.[20] The need for invasive monitoring intraoperatively depends on the severity of the cardiovascular or cerebrovascular pathology and the magnitude of the procedure.[19,20] Routine monitoring is appropriate for minor procedures (such as imaging or dermatologic procedures) and for patients with mild disease manifestations. More extensive monitoring, including intraarterial and bladder catheters, is indicated for major procedures with the potential for significant blood loss and for patients with more severe pathology, such as severe hypertension.[19,20] Neuromuscular blockade should be monitored with a peripheral nerve stimulator throughout the procedure.[19,20] As the spinal cord or peripheral nerves are not known to be involved, regional anesthesia is not contraindicated.[19]

Postoperatively, a short observation period is adequate following minor procedures in mildly affected patients. However, the patient should be admitted for monitoring and treatment after more extensive procedures or if the patient has significant organ dysfunction.[19] Except for specific indications, such as cessation of anticonvulsants following placement of electrocorticography grids and strips prior to resection of a seizure focus, baseline medical treatment should generally be resumed as soon as possible following the procedure.[19] Postoperative complications, which may be related to either the surgery or the TSC pathology itself, may include seizures, severe hypertension, and bradyarrhythmias.[19]

Neurologic Considerations

Preoperative evaluation should include determination of the nature of the seizure disorder, current anticonvulsant medications and blood levels of these drugs, degree of mental retardation, behavioral impairments, and extent of patient cooperation. Increased intracranial pressure secondary to intracranial lesions should also be excluded, and neuraxial anesthesia should not be performed in patients with increased intracranial pressure.[20] Anticonvulsant therapy should be optimized prior to the procedure and continued until the morning of surgery and throughout the perioperative period.[19,20] The prevention of seizures should be a goal of anesthetic management.[20,21]

The high likelihood of mental retardation, developmental delay, or behavioral problems necessitates certain precautions in preparation for surgery. Parental presence and involvement in simple preoperative tasks, such as monitor placement, are helpful in reducing anxiety levels associated with separation in both parent and child.[13] Pharmacologic sedation with agents such as intravenous or oral midazolam can be beneficial in patients with TSC to alleviate anxiety and facilitate intravenous catheter placement.[19]

Notable pharmacokinetic and pharmacodynamic interactions exist between antiepileptic drugs (AEDs) and the drugs commonly used in anesthesia, and these interactions affect both drug efficacy and seizure risk intraoperatively.[22] The most significant mechanism of interactions involves the induction and inhibition of the cytochrome P450 isoenzymes in hepatic metabolism by AEDs.[22,23] AEDs with enzyme-inducing properties accelerate metabolism of drugs

used in anesthesia, leading to decreased plasma concentrations and increased requirements of these drugs.[22,23] Enzyme-inducing AEDs include older-generation drugs such as carbamazepine, phenytoin, phenobarbital, and primidone, as well as clonazepam and lamotrigine. AEDs with mixed inducer and inhibitor characteristics include felbamate, oxcarbazepine, and topiramate.[22,23] These agents most notably cause relative resistance to and higher requirements for opioids and nondepolarizing neuromuscular-blocking agents, in addition to immunosuppressants, antibacterials, amiodarone, beta-blockers, and calcium channel-blockers.[19,20,22,23] Valproate is an inhibitor of the hepatic microsomal enzyme system and thus leads to a reduction in required doses of anesthetic drugs. Ethosuximide, gabapentin, levetiracetam, tiagabine, and zonisamide have no reported enzymatic activity.[22,23] Competition for protein-binding sites also affects free drug levels. For instance, phenytoin, benzodiazepines, and valproate are highly protein bound.[23]

Many anesthetic agents possess proconvulsant or anticonvulsant properties that must be considered when selecting an anesthetic regimen.[22,23] Many reports have described both proconvulsant and anticonvulsant properties for practically every anesthetic agent; typically, lower doses of these agents are associated with proconvulsant tendencies.[23] Nitrous oxide can suppress epileptiform activity but can also result in myoclonus at hyperbaric pressures and in combination with isoflurane or halothane.[22] Sevoflurane and enflurane are reported to provoke seizure activity, while isoflurane and desflurane appear to have primarily anticonvulsant properties and may even be used in refractory status epilepticus.[22,23] Opioids, including fentanyl, alfentanil, sufentanil, remifentanil, and morphine, induce seizure activity. Meperidine has the strongest association with myoclonus and tonic-clonic seizure activity.[22] The barbiturates (thiopental, methohexital, and pentobarbital), propofol, etomidate, and ketamine are reported to produce excitatory activity at lower doses, but they act as anticonvulsants at higher doses.[22] The benzodiazepines (diazepam, midazolam, and lorazepam) are potent anticonvulsants and are widely used to terminate status epilepticus.[22] Local anesthetics cross the blood-brain barrier and can cause generalized convulsions at higher doses.[22] The nondepolarizing neuromuscular-blocking agents do not appear to have either proconvulsant or anticonvulsant activity, although laudanosine, a metabolite of atracurium, has been demonstrated to cause seizures in animal studies and should be used cautiously in patients with hepatic failure in which the half-life of laudanosine is prolonged.[22] Succinylcholine produces EEG activation but has not been associated with clinically apparent seizure activity.[22] Anticholinergics (atropine and scopolamine) can produce central cholinergic blockade, resulting in seizures as well as hallucinations, restlessness or stupor, coma, and apnea. Glycopyrrolate does not cross the blood-brain barrier and does not produce these effects.[22]

Cardiovascular Considerations

Preoperative cardiovascular assessment includes an electrocardiogram in all patients to rule out dysrhythmias, conduction defects, or preexcitation.[20] Echocardiography and chest radiography are performed in patients in whom heart disease is suspected to exclude congenital heart disease and congestive heart failure caused by rhabdomyomas.[19,20] Intraoperative course may be complicated by dysrrhythmias.[24] The need for inotropic or chronotropic medications and the cardiovascular side effects of pharmacologic agents should be assessed.[19] Prophylactic antibiotics should be given to patients with cardiac tumors or congenital heart disease.[20] Hypovolemia resulting from massive hemorrhage should be prevented.[21]

Pulmonary and Airway Considerations

Preoperative evaluation of the upper airway and lungs should include determination of the presence of upper airway lesions and the exclusion of pneumothorax. If pulmonary involvement is suspected, chest radiography, pulmonary function tests, and arterial blood gas analysis should be done to assess the need for postoperative ventilation and intensive care unit admission.[19,20] Upper airway lesions, including nodular tumors, fibromas, and papillomas, may involve the tongue, palate, pharynx, or larynx and are present in 11% of patients with TSC.[19,24] They may cause significant obstruction and have the potential to bleed.[20] Airway management might be complicated by these lesions, and alternatives to direct laryngoscopy should be taken into consideration.[20] The preferred approach in patients with airway lesions is an awake fiber-optic intubation, although an asleep fiber-optic intubation is possible in a pediatric or mentally impaired patient who is breathing spontaneously.[20] Two successful methods that have been described include sevoflurane induction followed by fiber-optic intubation and utilization of dexmedetomidine for awake fiber-optic intubation.[20] In all patients with complicated airways, the American Society of Anesthesiologists guidelines should be consulted. A difficult airway cart and equipment for emergency tracheostomy should be available.[20] The decision to intubate the trachea and the timing of extubation should be made according to the size of

the upper airway masses, the extent of pulmonary disease, and the magnitude of the surgery.[19] The prevention of pneumothorax caused by barotrauma is attempted by maintaining a low tidal volume and low peak inspiratory pressure.[21] Positive end-expiratory pressure and nitrous oxide should also be avoided, as nitrous oxide may expand the airspace and cause rupture in patients with pulmonary cysts.[21]

Renal Considerations

Preoperative renal assessment should include measurement of blood urea nitrogen, creatinine, electrolytes, and blood pressure to gauge renal function and to rule out associated hypertension.[13,19,20] Intraoperative management involves avoiding renal insults and maintaining normovolemia and normotension to avoid decreases in renal perfusion and cardiac output.[25] The anesthesiologist must remain cognizant of the many potential complications of renal failure, such as anemia, altered platelet function and uremic coagulopathy, and metabolic derangements, and how these will affect perioperative management.[25]

Renal failure in patients with TSC, as in all cases of renal failure, can affect drug absorption, volume of distribution, plasma protein binding, metabolism, and elimination.[25-28] Water-soluble metabolites of anesthetic agents, if they possess even a fraction of the pharmacologic activity of the parent drug, may accumulate and prolong clinical effects in renal failure.[27] Drugs that are excreted unchanged by the kidneys may have a protracted elimination half-life in cases of renal failure.[27] Diminished albumin concentration and reduced protein binding secondary to uremia cause highly protein-bound drugs to exhibit amplified clinical effects.[26,27]

The nonvolatile products of metabolism of inhaled anesthetics are eliminated almost entirely by the kidneys.[28] However, impaired renal function does not alter the response to these agents, as reversal of their effects is dependent upon pulmonary excretion.[28] Enflurane is biotransformed into inorganic fluoride, the levels of which are lower than the nephrotoxic threshold.[28] However, as renal failure has been reported after enflurane use in patients with renal dysfunction, enflurane may be best avoided.[26] Although sevoflurane is also biotransformed, <4 minimum alveolar concentration hours of the agent is not associated with an increased risk of renal toxicity.[26] Desflurane and isoflurane are not associated with renal toxicity and are suitable choices in patients with renal failure.[26] Inhaled anesthetics generally cause a transient, reversible depression in renal function with reductions in glomerular filtration rate, renal blood flow, urine output, and urinary excretion of sodium.[28]

Thiopental requires a decreased induction dose and rate of administration secondary to an increased volume of distribution and reduced plasma protein binding, and its free fraction is nearly doubled in renal failure.[26,27] The pharmacokinetics or clinical effects of ketamine are not altered by poor renal function, as ketamine is less extensively protein bound.[27] Etomidate has a larger free fraction in renal failure, but the decreased protein binding does not appear to change its clinical effects.[27] Propofol is pharmacokinetically unaffected by renal failure; however, renal failure does require a considerably higher induction dose associated with a bispectral index value of 50 and an appreciably shorter time period between termination of propofol infusion and eye opening as compared to controls.[26] Nevertheless, propofol's effects are not reported to be prolonged.[27] The benzodiazepines, generally highly protein bound, may have their effects potentiated in renal failure secondary to an increased free fraction in plasma.[27] For midazolam, 60%-80% is excreted as its active alpha-hydroxy metabolite, which may accumulate following prolonged infusions.[27] Similarly, diazepam, lorazepam, and alprazolam cause increased sedation in patients with kidney disease.[27] Dexmedetomidine, although primarily hepatically metabolized, causes prolonged sedation in subjects with impaired kidney function, likely because of reduced protein binding.[27]

Opioids do not have direct toxic effects on the kidney, but they do possess an antidiuretic effect that may result in urinary retention.[26] Renal failure does not alter the pharmacokinetics of morphine in single doses, but chronic administration results in accumulation of the active metabolite morphine-6-glucuronide that has potent analgesic properties and may cause delayed onset of sedation and respiratory depression.[26,27] The decreased protein binding in renal patients necessitates a reduction in the initial dose and careful monitoring of respiration.[26,27] Meperidine and hydromorphone are metabolized to the neurotoxic normeperidine and hydromorphone-3-glucuronide, respectively, which are renally excreted and should be avoided in patients with renal failure.[26,27] The elimination half-lives of oxycodone, codeine, and dihydrocodeine are prolonged in renal dysfunction, necessitating reduced dosing or avoidance of these agents.[26] Fentanyl undergoes hepatic metabolism with no active metabolites, has an unchanged free fraction and short redistribution phase, and is therefore a good choice in renal failure.[26,27] Despite alfentanil's reduced protein binding in renal dysfunction, the total and infusion doses remain similar to

those for patients with normal renal function, as its elimination half-life and clearance are unchanged.[27] Remifentanil is rapidly metabolized by blood and tissue esterases to a minimally active metabolite, and renal failure does not affect the drug's clearance.[27] In terms of other analgesic agents utilized in the perioperative period, acetaminophen is considered safe in moderate doses, while the NSAIDs will likely cause more adverse effects than potential benefits in patients with renal dysfunction.[26]

Of all the drugs used in anesthetic practice, muscle relaxants are most likely to produce prolonged effects in renal failure.[27] With the exception of succinylcholine, atracurium, cisatracurium, and mivacurium, this class of drugs relies heavily on renal excretion.[27] In the case of renal dysfunction, most nondepolarizing muscle relaxants must be either hepatically excreted or metabolized to inactive forms to terminate their activity.[27] In general, the initial dose required to produce neuromuscular blockade is increased and the dose required to maintain the block is reduced in patients with renal failure.[26] Succinylcholine may be utilized as part of a rapid-sequence intubation technique if a patient's serum potassium level is normal, as its duration of action is not significantly prolonged in renal failure.[25,27] Atracurium and cisatracurium undergo enzymatic ester hydrolysis and spontaneous nonenzymatic (Hofmann) degradation, and chronic renal disease does not affect their elimination half-life, clearance, or duration of action.[27] Vecuronium's duration of action is prolonged in renal failure as a result of reduced plasma clearance, increased elimination half-life, and accumulation of its active metabolite, 3-desmethylvecuronium.[27] Results conflict regarding the pharmacokinetic sequelae of renal failure on rocuronium, but a wide variation in the duration of neuromuscular block has been reported.[27] The short-acting mivacurium is eliminated by plasma pseudocholinesterase, the activity of which is decreased in anephric patients, resulting in slower recovery from a bolus dose.[26,27] The reversal agent neostigmine, as well as the other clinically available anticholinesterases, has a reduced clearance and prolonged half-life in chronic kidney disease secondary to heavy reliance on renal excretion.[26,27]

CONCLUSION

TSC is a rare disease with a highly variable clinical presentation. Anesthesiologists and surgeons may encounter patients with TSC and should know how to manage the physiologic and pharmacologic complications associated with the disease in the perioperative period and beyond.

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