Tuberous Sclerosis Alliance

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I would like to take this opportunity to introduce you to the Tuberous Sclerosis Alliance (TS Alliance), the only national voluntary health organization dedicated to finding a cure for the genetic disorder known as tuberous sclerosis complex (TSC). Through the TS Alliance Outreach and Awareness Campaign, volunteers across the country are focusing on delivering up-to-date information on tuberous sclerosis complex as well as information about programs provided by the TS Alliance to their local physicians.

Every day, two children in the United States are born with tuberous sclerosis. Tuberous sclerosis is the only disease that can affect every organ in an individual's body. Individuals can be so mildly affected that they don't even know they have the disease until they have a child that is more severely affected. On the other hand, some individuals with TSC can have uncontrolled epilepsy, developmental delays, mental retardation and/or autism.

Enclosed is a fact sheet entitled *Treating Skin Disorders Associated with Tuberous Sclerosis,* as well as the most current recommended consensus guidelines for treatment of TSC dermatological lesions. Also enclosed are materials, including a sample letter and information sheet, that patients and physicians can submit to insurance companies supporting the medical necessity for the treatment of TSC skin lesions. Also enclosed is a list of other publications that the Tuberous Sclerosis Alliance offers along with the general *Understanding Tuberous Sclerosis* fact sheet. We hope that you will find this information helpful should you currently or one day diagnose or accept a patient with tuberous sclerosis complex.

The TS Alliance invites you and your colleagues to join our private list serve for physicians. We welcome you to subscribe to this private list serve free of charge. The discussion forum is confidential and limited to certified clinicians. The list serve enables colleagues to share experiences about caring for individuals with tuberous sclerosis. We encourage your participation!

In order to subscribe, simply e-mail me (yolanda.lee@tsalliance.org) the e-mail address at which you would like to receive list serve message postings, your mailing address (including clinic or hospital) and certification information. I will then add you to the list serve and you will receive a welcome message.

The TS Alliance is an ongoing resource for you and your patients. Please visit our Web site at www.tsalliance.org or call us at (800) 225-6872 to access additional information.

Sincerely,

Yolanda Lee

Yolanda Lee
Manager of Community Outreach

*fact*sheet

Tuberous Sclerosis Alliance

TUBEROUS SCLEROSIS COMPLEX Q & A'S

WHAT IS TUBEROUS SCLEROSIS COMPLEX?

Tuberous sclerosis complex (TSC) is a genetic condition commonly characterized by seizures and tumor growth in vital organs such as the heart, kidneys, lungs and skin. The disorder affects some people severely, while others are so mildly affected that it often goes misdiagnosed or undiagnosed. Some people with TC experience developmental delays, mental retardation or autism. However, there are also many people with TSC living independent, healthy lives and are enjoying challenging professions, such as doctors, lawyers, educators and researchers.

HOW MANY PEOPLE HAVE TS?

TSC is a genetic disorder that is estimated to affect nearly 50,000 people in the U.S., and more than 1 million worldwide. At least two children born each day will have TSC. Current estimates place TSC-affected births at 1 in 6,000 live births. There are also many undiagnosed cases of the disorder due to the obscurity of the disease and the mild symptoms some people have. TSC is as common as Lou Gehrig's Disease (ALS), but still virtually unknown by the general population.

HOW DOES A PERSON DEVELOP TSC?

TSC is transmitted either through genetic inheritance or as a spontaneous genetic mutation. Children have a 50 percent chance of inheriting it if one of their parents has the condition. At this point, only one-third of TSC cases are known to be inherited. The other two-thirds are believed to be a result of spontaneous mutation. The cause of these mutations is still a mystery.

WILL A CHILD BE MILDLY AFFECTED IF THEIR PARENT IS?

People with mild cases of TSC can have a child who is more severely affected. In fact, some people are so mildly affected that they may go undiagnosed until their more severely affected child receives a diagnosis of TSC.

WHAT CAUSES TSC?

Two genes have been identified to cause tuberous sclerosis. Only one of the genes needs to be affected for TSC to be present. The TSC1 gene is located on chromosome 9, the same chromosome carrying the gene that determines blood type. The TSC2 gene is located on chromosome 16. TSC occurs when an individual has a mutation in either the TSC1 or the TSC2 genes. The mutation can be inherited from one parent or can be a new mutation (sporadic event) that developed within the person.

Recent studies have shown that in familial cases of TSC (when there are two or more people with TSC in the family), about 50 percent of the families have a mutation in TSC1, and the other half contain a mutation in TSC2. The research has also shown that in sporadic cases of TSC (where there is no prior family history of TSC), more of the individuals have a mutation in the TSC2 gene than in the TSC1 gene.

HOW IS TSC DIAGNOSED?

Currently, diagnosis of TSC is based on clinical findings. Some of the tests used to assist in making the diagnosis are a brain MRI or CT Scan, renal ultrasound, echocardiogram, EKG, eye exam and a Wood's Lamp evaluation of the skin. A genetic test for TSC is not yet available. However, two centers in the U.S. offer genetic testing on a research basis with confirmation in a clinically certified laboratory.

ARE THE TUMORS CANCEROUS?

The tumors resulting from TSC are benign, but may still cause problems. Tumors that grow in the brain can block the flow of cerebral spinal fluid in the spaces (ventricles) in the brain. This can lead to behavior changes, nausea, headaches or a number of other symptoms. In the heart, the tumors are usually at their largest at birth, and then decrease in size as the individual gets older. These heart tumors (cardiac rhabdomyomas) can cause problems at birth if they are blocking the flow of blood or causing severe arrhythmia problems. Tumors in the eyes are not as common, but can present problems if they grow and block too much of the retina. Tumors in the kidney (renal angiomyolipoma) can become so large that they eventually take over all of the normal kidney functions. In the past, the patient was left alone

until they developed kidney failure. Today, doctors are more aggressive and remove individual tumors before they get too large and compromise healthy kidney tissue. Individuals with TSC very rarely (less than 2 percent) develop cancerous (malignant) kidney tumors.

WHAT IS THE NORMAL LIFE EXPECTANCY OF AN INDIVIDUAL WITH TSC?

Most people with TSC will live a normal life span. There can be complications in some organs such as the kidneys and brain that can lead to severe difficulties and even death if left untreated. To reduce these dangers, individuals with TSC should be monitored throughout their life by their physician for potential complications. Thanks to research findings and improved medical therapies, people with TSC can expect improved health care.

SINCE THERE IS NO CURE, WHAT CAN BE DONE?

Early intervention is helping to diminish developmental delays. Advancements in research are bringing new and improved therapeutic options. Surgery to remove tumors is helping to preserve the function of affected organs. Improved technology is helping to pinpoint the exact portions of the brain stimulating seizures, and is creating new therapies to help control seizures. Each day brings us closer to finding improved treatments.

People with TSC can stay informed of the advancements that are made by becoming a Tuberous Sclerosis Alliance member and receiving information and updates. Call us toll-free at (800) 225-6872 for more information on how to become a member.

*fact*sheet

Tuberous Sclerosis Alliance

TREATING SKIN DISORDERS ASSOCIATED WITH TUBEROUS SCLEROSIS

ASH LEAF SPOTS

There is currently no treatment available for ash leaf spots, or lightly colored skin patches that resemble ash tree leaves. Although there are normal numbers of pigment-producing cells in the spots, they are unable to produce sufficient amounts of pigment to create normal skin tone. New treatments are on the horizon for stimulating pigment production in the skin, and some of these treatments may eventually be applicable for the lightly colored skin patches of tuberous sclerosis (TS) patients.

There are special beauty aids available to cover de-pigmented skin. The following are a few of the cosmetic lines that can be contacted for more information:

-- Covermark Cosmetics at (800) 524-1120 or www.covermarkusa.com
-- Linda Seidel at (800) 590-5335 or www.lindaseidel.com
-- Dermablend at (800) 662-8011 or www.dermablend.com
-- Clinique products (at cosmetic counters nationally)

THE SHAGREEN PATCH AND FOREHEAD FIBROUS PLAQUE

Both of these less common skin lesions consist of an excess amount of fibrous tissue, similar to that found in scars. The shagreen patch is a section of thickened, elevated pebbly skin (like an orange peel) usually found on the lower back and nape of the neck. The forehead plaque is similar but is found on the forehead or scalp. Neither growth tends to cause problems (such as bleeding). Both of these skin lesions can be surgically removed but because of the resultant scar, it is usually not advised. There is currently no non-scarring method for the removal of these lesions and they tend to reoccur after removal. It is therefore recommended that the fibrous skin thickenings not be removed, unless they are causing severe problems.

ANGIOFIBROMAS OF THE FACE

Small flat red Aspots@ forming on the face, or a more generalized redness of the cheeks, nose and chin, are the first symptoms of angiofibromas. The redness is due to an excess number of blood vessels in the superficial part of the skin. Later, the lesions thicken and elevate, forming reddish-pink Abumps@, or angiofibromas. Although in some individuals the growths never develop past the red lesions, in most cases, the red lesions do develop into true, fibrous angiofibromas. There is currently no way to prevent the formation of the angiofibromas but there are promising ways to treat them.

Angiofibromas are best and most easily treated when they are in the early flat red spot stage. Treatment reduces or eliminates the red appearance of the skin and may decrease the likelihood of the growth getting larger. While a few individuals have reported no reoccurrence of their angiofibromas following treatment during this stage, there is good clinical evidence that removal of early, flat, red angiofibromas decreases the chance for the development of full-fledged, fibrous angiofibromas at the treated location. A **vascular (blood vessel) laser** is the best choice for treating the **flat** red spots. This laser is designed to destroy the blood vessel feeding the growing lesions in the skin with low risk of scarring. The laser light does not "see" the surrounding normal skin and is only absorbed by the red pigmentation. As a result, it is a good choice for the removal of early red angiofibromas. This laser treatment can either be performed in the office (if limited or if the patient is cooperative) or as an outpatient procedure. Treatment, which usually takes 10-20 minutes, causes moderate discomfort during the treatment. Topical anesthetics or oral sedation can be used in the office to minimize discomfort. The laser treatment can also be performed in conjunction with the sedation used for MRI evaluation. Following the treatment there is rarely any discomfort and usually no wound to care for. The full effect of a given treatment can be judged 6 - 8 weeks later and frequently if a lesion does not disappear, it can be retreated. Although there is no limit to the number of treatments that can be done, generally speaking, if no noticeable improvement is apparent after three treatments, one has to reassess either (1) the lesion that is being treated, (2) the laser chosen, or (3) the laser setting used. There is no age restriction for vascular laser treatment, but clinically it's been noted that the younger the child, the better the success of treatment.

For patients who already have well-developed fibrous angiofibromas, current available treatments include surgical removal, laser ablation (destruction) or dermabrasion. If only a few large angiofibromas are present, **surgical removal** is an option. It can be performed under local or general anesthesia in an outpatient setting. Although a permanent solution, the resultant scarring is also permanent.

Dermabrasion is a technique whereby elevated areas of the skin are "sanded" down to a level that is even with the surrounding skin. Successful outcome of this technique is heavily dependent on operator experience. Thus dermabrasion, as a method of skin resurfacing, has lost favor over the past several years due to the availability of laser resurfacing. The risk of residual scarring from dermabrasion is higher than laser resurfacing and is not recommended for individuals with facial angiofibromas.

If large areas of the face are affected, the most helpful options are **carbon dioxide (CO_2) or erbium:YAG laser surgery**. These lasers uniquely allow the surgeon to fine tune the light energy to remove angiofibromas without penetrating deeply into the dermal layer of the skin. This helps maximize treatment results while improving healing and minimizing scarring. Risk of scarring from laser treatment is lower than dermabrasion, however, because the CO_2 and erbium:YAG lasers destroy the epidermis and superficial dermis, some degree of scarring is unavoidable. Therefore, be sure to seek out an **experienced surgeon**. Do not be afraid to ask to see before and after pictures of patients the doctor has treated. Ask the surgeon how many patients he has treated specifically with Tuberous Sclerosis.

There are no age restrictions for CO_2 or erbium laser treatment. Generally younger children do not have many large raised angiofibromas but if they are seen, they can be treated at any age. Clinical evidence has shown that **there can be a rapid growth phase of the angiofibromas during puberty** therefore it is suggested that the child be seen and evaluated for treatment well before puberty begins.

Treatment with the CO_2 or erbium laser and is usually an outpatient procedure performed in a hospital or surgery center under general anesthesia under the supervision of an anesthesiologist. The laser treatment with the CO_2 laser is associated with minimal postoperative pain when the face is treated "open" with topical ointments. Clear and detailed postoperative instructions are important and careful attention to wound care is necessary for optimal skin healing. Be sure the doctor you select addresses these issues with you. Laser surgery is generally performed by either plastic surgeons or dermatologists. Reoccurrence is the greatest problem associated with removal of facial angiofibromas. As a result, laser surgery may need to be repeated.

PERIUNGUAL FIBROMAS AND GINGIVAL FIBROMAS

Periungual fibromas are angiofibromas that are located around the fingernails or toenails. People with periungual fibromas can develop pain when wearing shoes and walking or can distort and push up the nail itself causing infection and bleeding. These symptoms will require the removal of these lesions. **Surgical excision** is the most common technique for removal of these fibromas and can be combined with **CO_2 laser removal** to maximize effectiveness while limiting scarring and damage to the nail. Gingival fibromas are angiofibromas involving the gingiva (gums) of the mouth. They can cause bleeding or rarely, problems with eating.

All of the concerns about the removal of facial angiofibromas also apply to the removal of periungual and gingival fibromas. Choose your surgeon carefully and do not be afraid to ask questions. Generally, dentists and oral surgeons remove gingival fibromas and plastic surgeons, dermatologists and podiatrists remove periungual fibromas. These fibromas need to be completely excised or both can reoccur.

The willingness of insurance companies to cover the cost of these procedures is quite variable. Be sure to check with your insurance company before consulting with your doctor. If your insurance company refuses to cover the removal of facial angiofibromas, sometimes a letter from your doctor will help convince your insurance company to pay for the procedure. Form Insurance letters are available through the TS Alliance; these letters can be tailored for individual cases by the clinician.

IN SUMMARY

Although most skin disorders associated with TS are not curable, an experienced surgeon can remove troublesome lesions with favorable results. Additionally, with continued research into the control of blood vessel and fibrous tissue formation, the future looks bright for new, more effective treatments for skin disorders associated with TS.

Updated (2004) by Mark Mausner, M.D., a board-certified plastic surgeon affiliated with Georgetown Medical Center, Washington, D.C. Originally written by Joseph Yohn, M.D., a staff dermatologist, and an assistant clinical professor at the Bryan Medical Group, The Medical College of Ohio.

THE FOLLOWING LETTER IS TO BE COMPLETED BY A PHYSICIAN

Sample Insurance Letter Supporting the Medical Necessity of TSC Dermatology Treatment Procedures

To whom it may concern:

I am writing on behalf of (insert patient name) to provide information concerning the medical necessity for the treatment of facial angiofibromas in tuberous sclerosis complex (TSC). Treatment procedures for angiofibromas are considered THERAPEUTIC and NOT esthetic/cosmetic for patients with TSC.

(Insert patient name) was referred to me/ has been followed by me …(insert short patient history).

Examination revealed (provide description of results of examination)

For the medical reasons described in the accompanying materials, I am recommending…(insert treatment strategy).

The diagnosis code for this condition is…(insert diagnosis code). The procedure code would be…(insert procedure code). The patient/patient's parents are requesting pre-authorization for this procedure.

Thank you for your consideration. If you have any questions please do not hesitate to contact me.

Sincerely,

ADDITIONAL INFORMATION AND DETAILS FOR INSURANCE CARRIER

TREATMENT OF TUBEROUS SCLEROSIS COMPLEX DERMATOLOGICAL LESIONS

The information below provides answers to the following questions concerning the dermatological symptoms of tuberous sclerosis complex (TSC):

- What are the dermatological manifestations of TSC?
- Why is it medically necessary to treat TSC dermatological lesions?

Facial angiofibromas were first described in 1885 by Balzer and Menetrier. At this time, they were incorrectly termed adenoma sebaceum. We now know that the sebaceous glands are only passively involved, if at all. Facial angiofibromas are actually hamartomas (defined as benign, tumorous nodules of superfluous tissue). They have nothing to do with acnes, and do not respond to treatments for same. There is nothing the individual can do to prevent them. The typical facial angiofibromas are red to pink papules/nodules when they first appear, with a smooth, glistening surface. They are usually, but not always, bilaterally symmetrical, distributed over the centrofacial areas, particularly in the nasolabial folds, onto the cheeks in a butterfly fashion, and on the chin. They are sometimes seen on the forehead, scalp region, or even laterally on the face. The upper lip is usually spared, but lesions may be seen on the eyelids.

The tumors, found on the forehead and scalp, are large fibromas. These flesh-colored plaques are soft or compressible or doughy-to-hard lesions. Single large or multiple lesions may be seen. The angiomatous (highly vascular with a lot of blood vessels and appearing red) appearance is usually absent from these lesions; however, some forehead plaques can be bright red. The major findings in histopathology of the facial angiofibromas are dermal fibrosis and vasodilation. Elastic tissue is absent from these lesions. As the angiofibromas matures, the collagen becomes sclerotic and layered. Very often the facial angiofibromas will go from being small, soft, red nodules to become large, hard dark brown nodules with age, especially in individuals with dark skin complexion.

Facial angiofibromas may appear as early as the first year of life, but very often do not begin to appear until the child is four to six years of age, or older. As the individual enters puberty, the lesions may become even more numerous and prominent. However, once these tumors appear on the face, they persist for life, and usually increase in size, if they are not removed.
The Tuberous Sclerosis Alliance is currently developing a consensus document for appropriate treatment and removal of facial angiofibromas in individuals with TSC. In the past, dermabrasion and surgical removal were the only options for removal of facial angiofibromas. Widespread uses of laser treatments are proving to be more effective, less painful, and less likely to leave scars. Laser treatment is also more easily tolerated during the healing period. General anesthesia may be necessary dependent on the individual's symptoms and ability to cope with the procedure, especially for those individuals with TSC who have severe learning disabilities.

Two types of laser are commonly used on each patient, including the CO_2 laser for the larger, fibrous tumors, and the tunable dye, pulse-type laser for removing very small lesions and the redness of lesions. Sometimes these procedures are done in a two-step procedure, utilizing the CO_2 laser first and then the pulse laser 3 to 6 months later to normalize the color. Sometimes both of these lasers are used together. The expertise and skill of the physician, as well as his/her familiarity with TSC and these procedures, reduces the risk of scarring and optimizes outcome.

There is ongoing controversy about the age at which the facial angiofibromas should first be treated. There is clinical evidence that the earlier they are treated, while they are still soft, red and not fibrotic, the better the results. There appears to be slower regrowth and less scaring if the angiofibromas are removed early rather than waiting for them to become large and fibrotic. Once the facial angiofibromas are removed utilizing laser treatments, repeated laser treatments may be required. Since the facial angiofibromas are tumors, there is the chance that they will regrow. The growth rate and the interval between treatments will vary from one individual to the next, and should be tailored to the individual's medical needs.

There are several medical reasons why the facial angiofibromas should be removed, including the following:

1. These tumors are highly vascular and bleed very easily and profusely. It is often very difficult to prevent bleeding and to stop bleeding once it has started. This is particularly true for young males as they start to shave, and for any active individual who may run the risk of hitting or rubbing the lesions, resulting in bleeding.
2. Because the facial angiofibromas are so vascular, they are subject to infection if they are damaged and bleeding ensues. This is particularly dangerous around the nose and eye area because infection in this area ca easily be transferred into the intracranial blood vessels and carried to the brain.
3. Facial angiofibromas found on the eyelids may become so large as to obstruct vision and may bleed into the eye when the individual rubs their eyes and damages the tumor. These lesions should definitely be removed so as not to promote either visual obstruction or possible infection.
4. Facial angiofibromas found on the nose may become so large as to impair the use of glasses. Again, these lesions should definitely be removed so as not to prevent an individual from wearing their glasses and/or causing bleeding when the glasses are worn.
5. The psychological impact of having facial angiofibromas can be devastating to a young individual with TSC. These tumors may become very large and grotesque in appearance if they are not removed. Individuals with TSC have a difficult time coping with all of the various manifestations of the disease, and it is exceptionally hard to fend off taunts and teasing by peers who notice and make fun of the growths on the face. These tumors will only get worse with age – large, darker and more prominent. Therefore, it is imperative that these tumors are removed to increase the individual's quality of life.
6. Since these lesions are hamartomatous growths, these tumors are likely to grow back with time. The rate at which they return is different from one individual to another. For some, the tumors will not grow back several years, whereas other individuals will see their return within months. It is likely these tumors will have to be removed several times over the course of an individual's life. For a fortunate few, one procedure is sufficient and they do not return. Recent clinical experience shows that if the facial angiofibromas are removed early in life, they grow back more slowly, do not become as fibrous, hard and sclerotic, and they are easier and less expensive to remove.

TSC researchers are studying the function(s) of the TSC genes and their protein products, tuberin and hamartin, in skin cells to determine how the growth of facial angiofibromas may one day be halted and/or prevented.

The Tuberous Sclerosis Alliance would be happy to provide you with contact information for dermatologists and/or plastic surgeons who serve on the Professional Advisory Board and who would be happy to answer your questions about treatment approaches for facial angiofibromas.

Thank you for your consideration of this information. Hopefully, this information has clarified the importance of treatment for all person coping with these potentially disfiguring tumorous growths, facial angiofibromas. Please do not hesitate to contact the Tuberous Sclerosis Alliance if you would like additional information.

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