Skin Features of Tuberous Sclerosis Complex

The skin (often referred to as dermatologic or cutaneous) features of tuberous sclerosis complex (TSC) often play an important role in making the diagnosis of TSC in children and adults with the disease. Facial angiofibromas (previously and incorrectly called adenoma sebaceum) were included in the original diagnostic triad defined by Vogt (1908). Skin features of TSC may be seen in some infants who are suspected of having the disease. As an individual grows, additional skin lesions may appear that confirm a suspected diagnosis or provide the key piece to a diagnostic puzzle.

The age-related prevalence of skin features of TSC showed that 96% of the individuals had one or more of the skin lesions discussed below (Webb et al., 1996). There appears to be a trend toward early expression of hypomelanotic macules (white spots) and forehead fibrous plaques compared with the later development of facial angiofibromas and ungual fibromas. Shagreen patches are usually present by puberty if they are going to present in an individual with TSC. Ungual fibromas may also first appear during puberty.

The presence of the skin features of TSC is highly variable from one individual with TSC to the next, even within the same family where more than one individual has TSC. It is not known what causes the skin features to appear and/or why one individual will have them, and another will not. Ongoing research will help to shed light on the cause of the various skin features.

Hypomelanotic Macules

The hypomelanotic macules may be present at birth and usually persist throughout life. Sometimes the hypomelanotic macules are only visible with the use of a Wood's lamp – a special ultraviolet light that makes macules stand out against the surrounding normal skin. Hypomelanotic macules can become less obvious over time and may disappear in some cases, and individuals have reported new macules appearing later in life. The hypomelanotic macules are also referred to as ash leaf spots or white spots. The hypomelanotic macules can be distributed over the entire skin surface, but are most common on the trunk, limbs and buttocks. Involvement of the scalp and hair may result in a white patch of hair.

The number of hypomelanotic macules may vary from 3 or 4 to more than 100. In order to be useful in the process of making a diagnosis, the individual should have 3 or more hypomelanotic macules (one of the major features in the diagnostic criteria for TSC) (Roach et al., 1998). Hypopigmented macules are common in the general population, with one to three macules found in about 5% of the general population. They are usually 1.0 cm or more in length and can be any shape. The macules were once referred to as "ash-leaf spots" because they often resemble the shape of the European mountain ash tree. Sometimes numerous small macules may be present (especially on the arms and legs) that resemble confetti.

Although there are normal numbers of pigment (melanin)-producing cells in the hypomelanotic macules, they are unable to produce sufficient amounts of pigment to create normal skin tone. This results in an area of skin that is lighter than the surrounding skin. The hypomelanotic macules may not be visible in a fair-

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skinned individual, or they may be quite obvious in someone with darker skin tone, for example individuals of African-American descent.

There is currently no treatment available for hypomelanotic macules. New treatments are on the horizon for stimulating pigment production in the skin, and some treatments may eventually be applicable for the macules in individuals with TSC. Individuals with TSC should be especially careful to use at least SPF 45 sun screens when they will be in the sun as the hypomelanotic macules may be even more susceptible to sun burns than the surrounding skin.

Many individuals with TSC utilize special cosmetics to cover the hypomelanotic macules, especially if they are on the face. See the resource section of this information sheet for a list of companies that provide these products.

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 name is derived from the French phrase *peau chagrinée,* which means "skin with the appearance of untanned leather." There is no treatment for the shagreen patch, and they usually cause no problems for the individual other than being unsightly if they are in a location that can be easily seen by others. However, shagreen patches are most commonly found on the back, buttocks or upper thigh.

The forehead plaque is similar to the shagreen patch 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 advisable to discuss the benefits and risks of surgery with a plastic surgeon or dermatologist before making that decision.

There is currently no non-scarring method for the removal of these lesions, and they may reoccur after removal. The carbon dioxide (CO_2) laser may be helpful in treating some fibrous plaques.

Facial Angiofibromas
Facial angiofibromas are found in approximately 80% of individuals with TSC over 5 years of age. These skin lesions are hamartomas or non-cancerous growths. Small flat red "spots" forming on the face, or a more generalized redness of the cheeks, nose and chin, are the first symptoms of facial angiofibromas. The redness is due to an excess number of blood vessels in the superficial part of the skin. Later, before or during puberty, the lesions can thicken and elevate, forming reddish-pink "bumps," or facial angiofibromas. In some individuals with TSC the facial angiofibromas never develop, and in others they do not develop past the small red lesions. However, in most cases, the red lesions do develop into true, fibrous angiofibromas. They are commonly found bilaterally (on both sides) of the face and are symmetrical (the same on both sides), although there are reports of individuals with TSC who only have a few facial angiofibromas on one cheek or on one side of the nose. Facial angiofibromas are usually distributed across the cheeks and nose in what is referred to as a "butterfly fashion" and on the chin. Often the facial angiofibromas are found on the forehead, scalp or upper lip as well.

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 facial 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 of the blood cells. As a result, it is a good choice for the removal of early, red facial angiofibromas. This laser treatment can either be performed in the office (if limited or if the individual with TSC is cooperative) or as an outpatient procedure. Treatment, which usually takes 10-20 minutes, causes moderate discomfort if performed using only topical anesthetics or pain-free when using oral or intravenous sedation. 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 performed, generally speaking, if no noticeable improvement is apparent after two treatments, one has to reassess either (1) the nature of the lesion that is being treated; (2) the physician's choice of laser or experience with the laser; or (3) the type of anesthetic used and the laser setting that is used. There is no age restriction for vascular laser treatment, but clinically it's been noted that the younger the child (that is the flatter the lesion), the better the success of treatment.

For individuals with TSC who already have well-developed fibrous angiofibromas, current available treatments include surgical removal or laser ablation (destruction). 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.

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 facial angiofibromas without penetrating deeply into the dermal (deeper) 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 (top layers of skin) and superficial dermis, some degree of scarring is unavoidable. Therefore, be sure to seek out an experienced physician. Do not be afraid to ask to see before and after pictures of individuals with TSC the doctor has treated. Ask the physician how many individuals with TSC he has treated.

There are no age restrictions for CO_2 or erbium laser treatment. Generally, younger children do not have many large, raised facial 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 facial 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 is usually performed as an outpatient procedure in a hospital or surgery center under general anesthesia and 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 with topical ointments and left unbandaged. Clear and detailed postoperative instructions are very important and careful attention to wound care is necessary for optimal skin healing. Be sure the physician you select addresses these issues with you. Either plastic surgeons or dermatologists generally perform laser surgery. Reoccurrence is the greatest problem associated with removal of facial angiofibromas. As a result, laser surgery may need to be repeated.

Periungual Fibromas
Periungual fibromas are non-cancerous fibrous growths that are located around the fingernails or toenails. People with periungual fibromas on the toes can develop pain when wearing shoes, or the fibromas may distort the nail and push the nail up from the nail bed 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. These fibromas need to be completely removed or they may reoccur.

Gingival Fibromas
Gingival fibromas are fibrous (nodular) growths involving the gingiva (gums) of the mouth. They can cause bleeding or rarely, problems with eating. Gingival fibromas may occur more frequently in individuals with epilepsy who are taking phenytoin, an antiepileptic drug that causes gingival hyperplasia (overgrowth of the gums). 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.

Café-au-Lait Macules
These skin features are more often seen in individuals with another genetic disease, Neurofibromatosis 1 (NF1). Café-au-lait macules are essentially the opposite of hypomelanotic macules – they are oval or round, flat hyperpigmented (darker) areas of skin that are usually 1 to 5 cm in length. The presence of these lesions in individuals with TSC may mistakenly lead to a diagnosis of NF1, but only individuals with six or more café-au-lait macules should be considered for a diagnosis of NF1. Café-au-lait macules are found in the general population at about the same rate (16% of the total population) as in individuals with TSC (15.4%).

Soft Fibroma
Some individuals with TSC may have multiple or solitary, soft, baglike growths on the neck, trunk, or arms or legs. They may also have smooth papules on the neck, armpits (axillae) and near the flexure of the limbs. Another type of soft fibroma seen in individuals with TSC are one or more scattered small slightly raised, tiny papules (smaller than a pin's head) on the trunk or neck. These tiny skin lesions are the same color as the surrounding skin and resemble course "gooseflesh." If these fibromas are large they can be surgically removed. They may bleed excessively if they are torn off the skin, so an individual with TSC should always have a physician remove the fibroma.

Health Insurance Coverage for Skin Treatments in TSC
The willingness of health insurance companies to cover the cost of these procedures is quite variable. Be sure to check with your health insurance company before consulting with your

doctor. If your health insurance company refuses to cover the removal of facial angiofibromas, or any of the skin features of TSC, you may simply be talking to someone who considers this a cosmetic procedure and who does not understand the nature of the disease. Very often a letter from your doctor will help educate your health insurance company about TSC and the nature of the skin features of the disease, and they will agree to cover the costs of the procedure. Sample letters for you to use to educate your health insurance provider are available through the TS Alliance. These letters can be tailored by your physician for your individual needs.

Summary

Although most skin features of TSC are not curable, an experienced physician can remove the 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 the skin features of TSC.

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Webb DW, Clarke A, Fryer A, Osborne JP (1996) The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol 135:1-5

Resources:

There are cosmetics available to cover hypomelanotic macules. The following are a few of the cosmetic lines that can be contacted for more information:

Clinique
Phone: 1-800-419-4041
www.clinique.com

Covermark
Phone: 1-800-524-1120
(Spanish-speaking consultants available upon request to answer your questions)
www.covermarkusa.com

Dermablend
Phone: 1-877-900-6700
E-mail: askus@us.loreal.com
www.dermablend.com

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***Tuberous Sclerosis Alliance Information Sheets are intended to provide basic information about TSC. They are not treatment without first consulting a physician. The TS Alliance does not promote or recommend any treatment, therapy, institution or health care intended to, nor do they, constitute medical or other advice. Readers are warned not to take any action with regard to medical plan.*

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