R.C.P.U. NEWSLETTER

Editor: Heather J. Stalker, M.Sc.
Director: Roberto T. Zori, M.D.

R.C. Philips Research and Education Unit
Vol. XVII No. 1 A statewide commitment to the problems of mental retardation July 2005

R.C. Philips Unit ♦ Tacachale Center ♦ 1621 NE Waldo Rd. ♦Gainesville, FL 32609 ♦ (352)392-4104
E Mail: stalkhj@peds.ufl.edu ♦ zorirt@peds.ufl.edu
Website: http://peds.ufl.edu/genetics/

Tuberous Sclerosis

HISTORY

Tuberous sclerosis (TS) is an autosomal dominant disorder of cellular migration, differentiation, and proliferation. It is characterized by the widespread development of growths, usually described as hamartomas, in multiple systems of the body. The earliest description of TS was in a brief report presented by von Recklinghausen to the Obstetrical Society of Berlin in 1862. The disorder was given its name by Bourneville in 1880, when he gave the first detailed report of its neurologic symptoms and gross cerebral pathology. In 1920, van der Hoeve described the association of retinal hamartomas and TS. He observed that these hamartomas and other congenital tumors of the skin and viscera, link this disorder with neurofibromatosis and von Hippel-Lindau disease. He thus developed the concept of phakomatoses, which are disorders characterized by the presence of circumscribed lesions or phakomas (phakomas are congenital groupings of nevus cells found in various tissues, which have the potential of getting larger and forming real tumors).

Until recently, the clinical triad of Vogt consisting of: mental retardation, seizures, and adenoma sebaceum, was used for the diagnosis of TS. However, it has been shown that only a minority of individuals with TS actually exhibit one or more of these features, so a diagnosis based on the Vogt triad is now virtually obsolete. The National Tuberous Sclerosis Association has revised previous diagnostic criteria, and has created new guidelines for the diagnosis of TS. These guidelines are presented in Table 1.

CUTANEOUS FINDINGS

Hypopigmented spots or macules can be detected in patients of all ages, including neonates, and are observed most clearly with the use of a Wood's lamp. These lesions are present in approximately 90% of individuals with TS, and can have either a polygonal or an ash leaf shape; the ash leaf shape being most characteristic. Hypopigmented lesions are relatively common in the general population, and therefore they are given low weight in the diagnostic criteria. Other pigmentary abnormalities such as "confetti" lesions (areas of stippled hypopigmentation, typically on the extremities), and graying areas of the scalp hair or eyelids are also observed in TS.

Facial angiofibromas are hamartomas consisting of vascular and connective tissue elements and usually appear between 5 years of age and puberty as a few pink-red papules on the cheeks. They gradually become larger and more numerous, and may require repeated dermal abrasion for cosmetic purposes. These lesions are found in only 3/4 of TS patients, but they are considered pathognomonic of TS.

Ungual fibromas are also pathognomonic of TS and usually appear later in life, between 15 and 60 years of age. Ungual fibromas are nodular or fleshy lesions that arise adjacent to or below the nails.

The shagreen patch is a cluster of connective tissue hamartomas that are irregularly shaped and slightly elevated compared to the surrounding skin. They are typically found on the lower aspects of the back or on the flank area, and they have a greenish or reddish hue. The shagreen patch is found in only 20% to 30% of TS patients, and may not be apparent in young children.

Forehead fibrous plaques have a histological appearance similar to facial angiofibromas, ungual fibromas, and the shagreen patch, but they occur at a younger age (sometimes at birth), thus enabling earlier diagnosis.

OPHTHALMOLOGIC FINDINGS

The presence of multiple retinal hamartomas is considered pathognomonic of TS, but must be carefully evaluated to ensure that they are not retinoblastomas. Most retinal lesions are clinically insignificant, but some patients may experience visual impairment due to a large lesion. Rarely, a patient will have loss of vision due to hamartoma enlargement, vitreous hemorrhage, or retinal detachment. Pigmentary changes, called achromic patches, are also common retinal findings in TS.

CARDIOVASCULAR FINDINGS

Cardiac rhabdomyomas are common in infants with TS. These lesions are best classified as hamartomas and are typically multiple in number. Cardiac rhabdomyomas are not usually clinically important, although occasional patients have outflow obstruction of one or both ventricles. Most patients who do develop cardiac dysfunction present with heart failure soon after birth. Of all children presenting with signs or symptoms of cardiac rhabdomyomas, approximately 80% will be found to have TS. Clinically silent rhabdomyomas have been shown to diminish with age, and to sometimes disappear altogether.

RENAL FINDINGS

Renal angiomyolipomas are found in about 2/3 of individuals with TS. They are histologically benign tumors with varying amounts of fat, smooth muscle, and vascular tissue. Angiomyolipomas are not specific for TS, but many patients with these lesions also have other lesions that are indicative of TS. Bilateral tumors or multiple tumors per kidney are common, and the prevalence of tumors increases with age. Angiomyolipomas are usually clinically silent, but may rarely cause life-threatening hemorrhage. There is also a small risk of conversion of this renal lesion to a renal cell carcinoma.

Renal cysts, single or multiple, are also relatively common features of TS. In combination with angiomyolipomas, these cysts are considered to be pathognomonic of TS. Renal cysts are more common in children, whereas angiomyolipomas are seen more often in adults. These cysts are usually asymptomatic, but may lead to end stage renal disease with extreme hypertension in some instances.

NEUROLOGIC FINDINGS

The central nervous system involvement in TS includes characteristic cortical tubers, and subependymal nodules.

Cortical tubers disrupt and displace cortical organization, and their size and number correlates roughly with the degree of two major neurological manifestations of TS: seizures and mental retardation. Seizures and mental retardation are classic features of TS, but because they are nonspecific, neither is considered part of the diagnostic criteria. Studies have shown that approximately 80% of patients with TS have seizures, while about 50-60% of TS patients have some degree of mental retardation. Early onset seizures (generally less than 1 year of age) and generalized seizures are both associated with more severe mental retardation and a greater number of cortical tubers.

The subependymal nodules commonly seen in TS usually line the third ventricle in the brain. The subependymal nodules often calcify later in life, making their visualization with CT much easier. Some of these nodules may grow larger than 3cm in diameter, and these larger lesions are then called subependymal giant cell astrocytomas. Giant cell astrocytomas develop in about 6% to 14% of individuals with TS. Subependymal giant cell astrocytomas can cause severe clinical manifestations if the flow of cerebrospinal fluid is blocked, and may therefore require surgical removal.

Behavior disorders are a third major brain-related clinical manifestation of TS. Approximately 50% of children with TS are autistic. Attention-deficit hyperactivity disorder, hyperkinesis, and aggressive behavior are also common features of TS. Although many children with TS will have both mental retardation and behavior disorders, some children have behavioral problems without mental impairment.

OTHER FINDINGS

Pulmonary lymphangiomyomatosis is a rare feature of TS, occurring only in females, with an incidence of about 6%. Microhamartomatous rectal polyps occur in approximately 3/4 of all TS patients, and are usually numerous and asymptomatic. Clinically benign hepatic hamartomas are seen in about 1/4 of all children with TS, and dental enamel pitting is observed in approximately 90% of TS patients.

Table 1. Diagnostic Criteria for Tuberous Sclerosis

(adapted from Roach et al., 1992)

Primary Features

- Facial Angiofibromas*
- Multiple Ungual Fibromas *
- Cortical Tuber (histologically confirmed)
- Subependymal nodule or giant cell astrocytoma (histologically confirmed)
- Multiple calcified subependymal nodules (radiographic evidence)
- Multiple retinal astrocytomas

Secondary Features

- Affected first-degree relative
- Cardiac rhabdomyoma (histologic or radiographic evidence)
- Other retinal hamartoma or achromic patch*
- Cerebral Tubers (radiologic confirmation)
- Noncalcified subependymal nodules (radiologic confirmation)
- Shagreen patch*
- Forehead plaque*
- Pulmonary Lumphangiomyomatosis (histologic confirmation)
- Renal angiomyolipma (histologic or rediographic confirmati0n)
- Renal cysts (histologic confirmation)

Tertiary Features

- Hypomolanoitc macules*
- "Confetti" skin lesions*
- Renal cysts (radiographic evidence)
- Enamel pits in deciduous and/or permanent teeth
- Hamartomatous rectal polyps (histologic confirmation)
- Bone cysts (radiographic evidence)
- Pulmonary lumphangiomyomatosis (radiographic evidence)
- Cerebral white-matter heterotopias (radiographic evidence)
- Gingival fibroma*
- Hamartoma of other organs (histologic confirmation)
- Infantile spasms

*Histologic confirmation not required if lesion is clinically obvious

Definite dx – either one primary,two secondary or one secondary & two tertiary features
Probable dx – either one secondary and one tertiary or three tertiary features
Suspect dx – either one secondary or two tertiary features

PROGNOSIS

It is now recognized that approximately half of all individuals affected with TS have normal intellectual function. Children with TS who do not develop seizures in the first five years of life are less likely to have learning disabilities than those children with early onset seizures. Improvement in developmental progress upon seizure control is

commonly experienced. Males with TS tend to have a greater incidence of early onset seizures, and generally have a poorer outlook for seizure control and cognitive development.

Individuals with TS have only a slight decrease in overall survival compared to the general population. Most of the tumors associated with TS are not life threatening. Brain involvement (status epilepticus, obstructive hydrocephaly), renal involvement (renal failure, carcinoma, hemorrhage), and pulmonary complications (recurrent pneumothoraces, pneumonia) are the main causes of excess mortality in TS.

GENETICS OF TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis is one of the most common genetic conditions, with an incidence ranging from as high as 1/5800 to 1/10,000 births. TS is inherited in an autosomal dominant fashion, although approximately 60-80% of cases represent new mutations (first occurrences in a family). TS is characterized by a relatively high degree of penetrance (the majority of individuals who possess the TS gene will show some sign(s) of the condition), and extreme clinical variability, even within individuals of the same family.

Two genetic loci have been identified for TS, one on 9q34 (TS1 or hamartin) and one on 16p13.3 (TS2 or tuberin). Clinical testing is available for both of these genes, and the detection rate for mutations in individuals who have probably TS based on clinical criteria have ranged drom 60-85% in different clinical studies. In inherited TS, studies have shown that slightly less than half of the affected individuals are shown to have hamartin mutations and slightly more than half to have tuberin mutations. In sporadic cases, however, tuberin mutations appear to be significantly more common. No consistent phenotypic differences have been discovered between TS1 and TS2. A small group of patients with large deletions in the TS2 gene have deletions of significant enough size to also encompass the polycystic kidney disease gene (PKD), thus resulting in a combined phenotype. Loss of heterozygosity for chromosome regions including TS1 and TS2 has been shown in hamartomas analyzed from TS patients, and suggests a role for these genes as tumor suppressor genes. The patchy, focal nature of the tumors associated with TS may therefore be influenced by external factors which "knock out" the normal functioning allele in an individual whose constitutional genome already has one TS allele.

GENETIC COUNSELING

In order to provide accurate counseling and risk assessment, a thorough evaluation of the parents of an affected child (including physical and radiographic) must be performed. Since the phenotype is so variable, it is suggested that mutation analysis of TS1 and TS2 be performed in all instances before recurrence risk information is provided. If an identifiable mutation is found in the child, parents can be tested to determine if they carry the mutation or not. If parents are not found to carry the mutation, their risks are felt to be less than 2% for future pregnancies, but will not be zero due to the possibility of gonadal mosaicism in these genes. If the parents carry the TS mutation, then their risks are 50% in future pregnancies. In either of these instances, prenatal diagnosis by amniocentesis would be possible.

In cases where a mutation is not identified, but the parent appears to be affected, the risk for future children to be affected is 50%. If neither parent shows evidence of TS after a detailed physical evaluation, the child with TS is thought to represent a new mutation, and parents are usually told that there is a 2% recurrence risk of TS in future children. The child with TS will have a 50% risk of transmitting the condition to their children in either instance.

Cardiac rhabdomyomas provide a means of prenatal diagnosis of TS, via ultrasound imaging, but are rarely observed before 20 weeks gestation. The risk of TS increases with the number of tumors, being approximately 30% with a single tumor and 80% with two or more tumors. One recent study has also shown that prenatal head MRI is a useful tool in the diagnosis of fetuses with cardiac tumors.

One last issue to be considered is that of female TS patients during pregnancy. All anticonvulsant medications studied have been shown to have teratogenic effects. Women taking these medications for seizure control should be provided with information regarding these effects. On the other hand, the risk for fetal malformations seems to be lower in women who are seizure free. Hence, female TS patients should receive appropriate counseling before and during pregnancy.

SUPPORT ORGANIZATIONS

The National Tuberous Sclerosis Association (NTSA) provides a source for peer support, matching of individuals/families, referrals to local chapters or groups, and educational materials. For more information about NTSA contact:

The National Tuberous Sclerosis Association, Inc.
8000 Corporate Drive, Suite 120
Landover, MD 20785
1-800-225-6872

REFERENCES

1) Gomez, M. *Tuberous Sclerosis*. New York, NY: Raven Press, 1988.
2) Kwiatkowski D, Short P. Tuberous Sclerosis. *Arch Dermatol.* 1994;130:348-354.
3) Roach ES, Delgado MR. Tuberous Sclerosis. *Dermatologic Clinics.* 1995 Jan;13(1):151-161.
4) Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L. Diagnostic criteria: tuberous sclerosis complex. *J Child Neurol.* 1992;7:221-224.
5) Sonigo P, Elmalch A, Fermont L, Delezoide AL, Mirlesse V, Brunelle F. Prenatal MRI diagnosis of fetal cerebral tuberous sclerosis. *Pediatr Radiol.* 1996;26(1):1-4.
6) Webb DW, Osborne JP. Tuberous sclerosis. *Arch Dis Child.* 1995 Jun;72(6):471-474.
7) Mizuguchi M, Kato M, Yamanouchi H, Ikeda K, Takashima S. Loss of Tuberin from Cerebral Tissues with Tuberous Sclerosis and Astrocytoma. *Ann Neurol.* 1996 Dec;40(6):941-944.

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for
mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health, Children's Medical Services.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

Acknowledgments:

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

The RCPU Newsletter is funded by the Raymond C. Philips Research and Education contract with the Department of Health, Children's Medical Services.

University of Florida
Pediatric Genetics
Box 100296
Gainesville, FL 32610

Non Profit Organization
US POSTAGE PAID
Florida, Gainesville
PermitNo.94