# Imaging in Tuberous Sclerosis Complex

Imaging in Tuberous Sclerosis Complex
PhD Thesis, University of Utrecht, the Netherlands – with a summary in Dutch
ISBN 978 94 6159 040 4



Production: Datawyse | Universitaire Pers Maastricht

Financial support by Anagha P. Parkar, Guerbet Nederland B.V., Novartis Pharma B.V., Röntgen Stichting Utrecht, Sectra Benelux, and Stichting Tubereuze Sclerosis Nederland for the publication of this thesis is gratefully acknowledged.

# Imaging in Tuberous Sclerosis Complex

## Beeldvorming bij Tubereuze Sclerose Complex (met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar te verdedigen
op dinsdag 26 april 2011 des middags te 4.15 uur

door

**Miraude Emmanuela Antoinette Petra Maria Adriaensen**

geboren op 21 augustus 1978
te Deurne

**Promotor**
Prof. dr. M. Prokop

**Co-promotoren**
Dr. C.M. Schaefer-Prokop
Dr. B.A. Zonnenberg

# Contents

# 1

# General introduction

## Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an inheritable multiorgan disease. It is an autosomal-dominant neuro-cutaneous disorder characterized by tumor-like malformations involving many organ systems including brain, kidneys and skin (1).

The first illustration of a skin lesion, later to be found typical for TSC, was published in the 'Atlas of Diseases of the Skin' by Rayer in 1835 (2). The name of this skin lesion changed over time from facial 'végétations vasculaires' to 'adenoma sebaceum' to the currently used term facial angiofibromas (3;4). Von Recklinghausen was the first to describe a case of TSC. In 1862 he reported the autopsy findings in a newborn with cardiac 'myomata' and 'sclerotic' brain lesions (5). The term tuberous sclerosis was first mentioned by Bourneville in 1880 when he reported the neurologic and gross pathologic findings in two patients who died of epilepsy (6). In 1908 Vogt recognized the association of seizures, mental retardation, and adenoma sebaceum and thus made it possible to diagnose TSC during a patient's life time (7).

The diagnosis of TSC is still made clinically. However, the classical diagnostic triad of seizures, mental retardation, and facial angiofibromas occurs in less than half of the patients as the expression and the severity of the disease show substantial variation within as well as between families (8;9). Therefore, a clinical scoring system was developed. Already in 1979 Gomez et al proposed a set of diagnostic criteria for TSC which afterwards have been revised multiple times (2;10–12). The diagnostic criteria for TSC were last revised during the TSC consensus conference held in 1998 (12). These revised clinical diagnostic criteria divide the diagnostic criteria for TSC into major features and minor features. No single diagnostic feature is considered pathognomonic for TSC anymore. The diagnosis of definite TSC requires the presence of two major features, or of one major and two minor features. Major features are facial angiofibromas or forehead plaques, shagreen patch, three or more hypomelanotic macules, nontraumatic (peri)ungual fibromas, lymphangioleiomyomatosis, renal angiomyolipoma, cardiac rhabdomyoma, multiple retinal nodular hamartomas, cortical tuber, subependymal nodules, and subependymal giant cell astrocytomas. The list of minor features includes less specific findings and less substantiated signs (Table 1) (12).

**Table 1** Revised Diagnostic Criteria for Tuberous Sclerosis Complex

| |
|---|
| **Major features** |
| Facial angiofibromas or forehead plaque |
| Nontraumatic ungual or periungual fibroma |
| Hypomelanotic macules (three or more) |
| Shagreen patch (connective tissue nevus) |
| Multiple retinal nodular hamartomas |
| Cortical tuber [a] |
| Subependymal nodule |
| Subependymal giant cell astrocytoma |
| Cardiac rhabdomyoma, single or multiple |
| Lymphangiomyomatosis [b] |
| Renal angiomyolipoma [b] |
| **Minor Features** |
| Multiple, randomly distributed pits in dental enamel |
| Hamartomatous rectal polyps [c] |
| Bone cysts [d] |
| Cerebral white matter radial migration lines [a, d, e] |
| Gingival fibromas |
| Nonrenal hamartoma [c] |
| Retinal achromic patch |
| 'Confetti' skin lesions |
| Multiple renal cysts [c] |
| **Definite Tuberous Sclerosis Complex** |
| Either two major features or one major feature plus two minor features |
| **Probable Tuberous Sclerosis Complex** |
| One major plus one minor feature |
| **Possible Tuberous Sclerosis Complex** |
| Either one major feature or two or more minor features |

[a] When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.
[b] When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned.
[c] Histologic confirmation is suggested.
[d] Radiographic confirmation is sufficient.
[e] One panel member felt strongly that three or more radial migration lines should constitute a major sign.

The birth incidence of TSC is approximately one in 5,000 to 10,000 live births (13). However, the true birth incidence is still not known due to the possibility of undiagnosed individuals who are only mildly affected or asymptomatic (9;14).

Since 1995, our institution is a nationwide referral center for patients with TSC. In August 2008, our institution followed 327 patients with TSC. Individuals with TSC are identified through symptoms, case finding by physicians working in institutions for mentally disabled, and family screening. According to national and international guidelines patients with TSC undergo regular imaging at our radiology department (15–17).

## Outline of the thesis

Aim of this thesis was to initiate a systematic evaluation of imaging in patients with tuberous sclerosis complex followed at our institution. This thesis focused on imaging of the heart, the lungs and the brain.

We noticed a discrepancy between our national TSC guidelines and the recommendations for diagnostic evaluation in TSC developed during the TSC consensus conference in 1998 with regard to screening for cardiac rhabdomyomas by echocardiography. Chapter 2 reports a study that assessed the frequency of abnormal echocardiographic findings in a cohort of patients with TSC referred to our cardiology department for screening echocardiography.

Patients with TSC undergo regular computed tomographic (CT) scanning of the abdomen to monitor renal angiomyolipomas. In daily practice we noticed focal areas of fat within the myocardium in the caudal portions of the heart depicted at abdominal CT scans. Chapter 3 reports a case-control study that examined the morphologic characteristics on CT of such focal fatty foci in the myocardium of patients with TSC. Chapter 4 shows a case of fatty foci in a patient with TSC as seen on magnetic resonance imaging (MRI). Chapter 5 describes the histopathologic finding of focal areas of mature fat cells in the myocardium of patients with TSC.

Lymphangioleiomyomatosis (LAM) is characterized by diffusely distributed pulmonary thin-walled cysts with intervening normal lung parenchyma. According to the literature almost all patients are female. In daily practice we noted male patients with thin-walled cysts in the basal portions of the lungs depicted at abdominal CT scans. Chapter 6 reports a study that investigated the gender-specific prevalence of thin-walled cysts in the lung parenchyma of adult patients with TSC.

In the literature the reported prevalence of subependymal giant cell tumors (SGCT) in TSC varies from 6% to 19%. Chapter 7 reports a study that investigated the prevalence of radiologic evidence of SGCT in our cohort of patients with TSC. In addition a systematic review of the English language medical literature regarding the prevalence of SGCT in TSC was performed.

Finally, a summary of this thesis in English and in Dutch is provided and suggestions for future research are discussed.

## References


1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355(13):1345–1356.
2. Gomez MR. History of Tuberous Sclerosis Complex. In: Gomez MR, Sampson JR, Whittemore VH, editors. Tuberous Sclerosis Complex: developmental perspectives in psychiatry. New York: Oxford University Press, 1999: 3–9.
3. Balzer F, Ménétrier P. Étude sur un cas d'adénomas sébacés de la face et du cuir chevelu. Arch Physiol Neurol Pathol 1885; 6:564–576.
4. Pringle JJ. A case of congenital adenoma sebaceum. Br J Dermatol 1890; 2:1–14.
5. Recklinghausen von F. Ein Herz von einem Neugeborene welches mehrere theils nach aussen, theils nach den Höhlen prominirende Tumoren (Myomen) trägt. Monatschr Geburtskd Frauenkr 1862; 20:1–3.
6. Bourneville DM. Sclérose tubéreuse des circonvolutions cérébrales: idiotie et épilepsie hémiplégique. Arch Neurol 1880; 1:81–91.
7. Vogt H. Zur Diagnostik der tuberosen sklerose. Z Erforsch Behandl Jugeundl Schwachsinns 1908; 2:1–16.
8. Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of expression in tuberous sclerosis. J Med Genet 1993; 30(1):41–43.
9. Schwartz RA, Fernandez G, Kotulska K, Jozwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. J Am Acad Dermatol 2007; 57(2):189–202.
10. Osborne JP. Diagnosis of tuberous sclerosis. Arch Dis Child 1988; 63(12):1423–1425.
11. Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L. Diagnostic criteria: tuberous sclerosis complex. Report of the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association. J Child Neurol 1992; 7(2):221–224.
12. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13(12):624–628.
13. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991; 615:125–127.
14. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet 1998; 351(9114):1490.

15. Halley DJJ, Hoff M, Hubbeling A, Lindhout D, Maat-Kievit JA, Mulder J et al. Wat is Tubereuze Sclerose Complex? 2nd ed. Zeist, the Netherlands: Stichting Tubereuze Sclerose Nederland (STSN), 2004; 1–59.
16. Zonnenberg BA, Stroink H, Lequin MH, Oranje AP, van Dorp DB, Siderius EJ et al. Leidraad voor de medische begeleiding van kinderen met tubereuze sclerose. Velp, the Netherlands, 1999; 1–21.
17. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol 1999; 14(6):401–407.

# 2

# Echocardiography screening results in patients with tuberous sclerosis complex

*Texas Heart Institute Journal, 2010; 37(3):280-283*

Miraude EAPM Adriaensen, M.D., MSc.
Maarten JM Cramer, M.D., Ph.D.
Madelon EE Brouha, M.D.
Cornelia M Schaefer-Prokop, M.D., Ph.D.
Mathias Prokop, M.D., Ph.D.
Pieter AFM Doevendans, M.D., Ph.D.
Bernard A Zonnenberg, M.D., Ph.D.
Harm HH Feringa, M.D., Ph.D.

## Abstract

**Purpose:** To examine the frequency of abnormal findings in echocardiography in patients with tuberous sclerosis complex (TSC).
**Methods:** In a retrospective cohort study, we included all patients with known TSC who had been sent to our cardiology department for echocardiographic screening from 1995 through August 2003 (n=56). Two research scientists independently reviewed the reports of the echocardiographic screening examinations for abnormal findings. We used descriptive statistics, the Mann-Whitney U test, and Chi-square-test.
**Results:** The mean age of included patients in the study was 35 years (range, 12–73 yr); 23 patients were male. Abnormal findings were seen in 22 patients (39%). The most common abnormal findings were focal areas of increased intramyocardial echogenicity, which were seen in 16 patients (29%). The clinical consequence of this finding is still unknown.
**Conclusion:** Echocardiographic abnormalities are common in patients with TSC.

## Introduction

Tuberous sclerosis complex (TSC) is an inheritable multiorgan disease. It is an autosomal-dominant neurocutaneous disorder characterized by tumor-like malformations involving many organ systems including the brain, heart, kidneys, and skin (1). The birth incidence of TSC is approximately 1 per 5,000 to 10,000 live births (2). The diagnosis of TSC is made clinically. However, the expression and the severity of the disease show substantial variation within as well as between families (3). The classical diagnostic triad of seizures, mental retardation, and facial angiofibromas occurs in fewer than half of the patients. Therefore, a clinical scoring system was developed that divides the diagnostic criteria for TSC into major and minor features (4).

Single or multiple cardiac rhabdomyomas are considered a major feature (4). More than half of all infants with TSC show evidence of cardiac rhabdomyomas on echocardiography (5-7). However, rhabdomyomas tend to regress over time (6;8-11).

Since 1995, our institution has been a national referral center for patients with TSC. A multidisciplinary approach is used according to Dutch national TSC guidelines (12;13), which recommend at least 1 echocardiogram to screen for cardiac rhabdomyomas in patients with TSC. However, the recommendations for diagnostic evaluation in cases of TSC as defined at the Tuberous Sclerosis Consensus Conference in 1998 specify that echocardiography be performed during initial testing only if cardiac symptoms are present or if confirmation of a suspected cardiac lesion is needed; and that echocardiography be performed during repeat testing if cardiac dysfunction has occurred (14).

The purpose of this study was to determine the frequency of abnormal findings seen upon screening echocardiography in a relatively large cohort of patients with TSC.

## Patients and Methods

### Study Design

We performed a retrospective cohort study that included all patients with TSC who were referred by our TSC outpatient clinic to our cardiology department for echocardiographic screening from the start of our outpatient TSC clinic in 1995 through August 2003. Our institutional review board approved this retrospective study and

patient informed consent was waived. Echocardiographic screening reports were available for all 56 patients included in this study.

### Echocardiographic Data Acquisition

All patients underwent a standard screening echocardiographic examination at our cardiology department at some time during the study period. Transthoracic echocardiography was performed with a S3 transducer, range 1–3MHz (Philips HP Sonos 5500® imaging system, Koninklijke Philips Electronics N.V.; Eindhoven, the Netherlands) in multiple planes, according to standard clinical practice. Parasternal long- and short-axis and apical 4-chamber views were obtained. All echocardiographic studies were performed by 1 of 2 experienced sonographers, each of whom had more than 10 years of echocardiographic experience.

### Echocardiographic Data Review

Two research scientists (MA and MB) independently studied the written reports on the screening echocardiographic examinations for abnormal findings. Abnormal findings for each patient were recorded on a case-record form. The research scientists were blinded to each other's forms. Cases in which the findings of the two reviewers disagreed were re-evaluated, and a final decision was made.

### Data Analysis

Descriptive statistics were used to describe patients' characteristics and the number of findings that were abnormal upon screening echocardiography. We calculated an unweighted kappa statistic to evaluate interobserver agreement between the 2 research scientists. We used the Mann-Whitney U test to compare means between groups and Chi-square-test to compare proportions. Analyses were performed with Excel for Windows (Microsoft, Redmond, Wash) and SPSS version 15 (SPSS, Inc.; Chicago, Ill).

## Results

All 56 patients had TSC according to the criteria set forth by the consensus conference in 1998 (4). Mean patient age was 35 years (range, 12–73 yr). Thirty-three of

the 56 patients were female (59%). Abnormal findings on screening echocardiographic examinations were seen in 22 out of 56 patients (39%). Interobserver agreement for detection of abnormal findings in screening echocardiography reports was excellent (K = 1).

The most common abnormal finding on screening echocardiographic examination in these patients with known TSC was focal areas of abnormal intramyocardial hyperechogenicity (Figs. 1 and 2), which were seen in 16 of 56 patients (29%) (Table 1). Significantly more foci were found in males (10/23 = 43%) than in females (6/33 = 18%) (p=0.045). Intramyocardial hyperechogenic foci were located in the interventricular septum, the left ventricular wall, and the papillary muscles. Multiple lesions were seen in 5 of these 16 patients. Patients with focal areas of abnormal intramyocardial hyperechogenicity (mean age, 27 yr; range, 16–45 yr) were on average younger than were patients without these abnormalities (mean age, 38 yr; range, 12–73 yr)(p = 0.007).

**Table 1.** Abnormal findings in echocardiographic screening in patients with tuberous sclerosis complex*

| **Abnormal finding** | **Number of patients** |
|---|---|
| | **16** |
| **Focal areas of increased intramyocardial echogenicity** | |
| Multiple focal areas of increased intramyocardial echogenicity | 5 |
| Valvular abnormalities** | 3 |
| Abnormalities of myocardial function** | 2 |
| | **6** |
| **Isolated abnormalities** | |
| Valvular abnormalities | 3 |
| Abnormalities of myocardial function | 3 |

* The total number of patients who had abnormal findings was 22 (out of 56 screened).

** These abnormal echocardiographic findings were presumably unrelated to the focal areas of increased myocardial echogenicity.

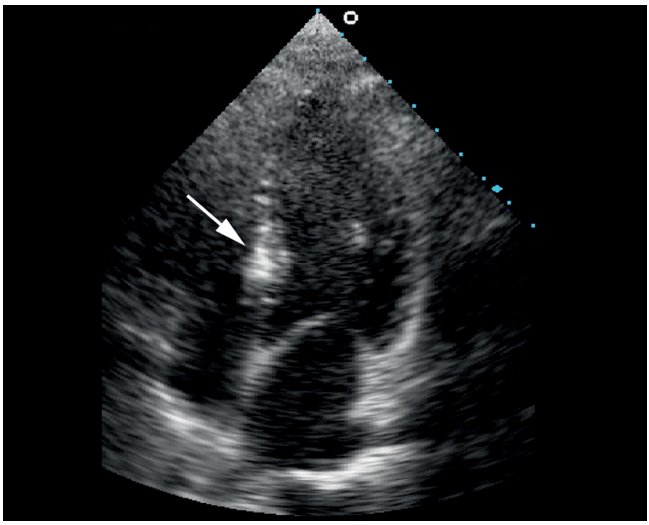


**Figure 1.** Echocardiogram (4-chamber view) of a 20-year-old woman with tuberous sclerosis complex shows a focal area of increased echogenicity in the interventricular septum (arrow).

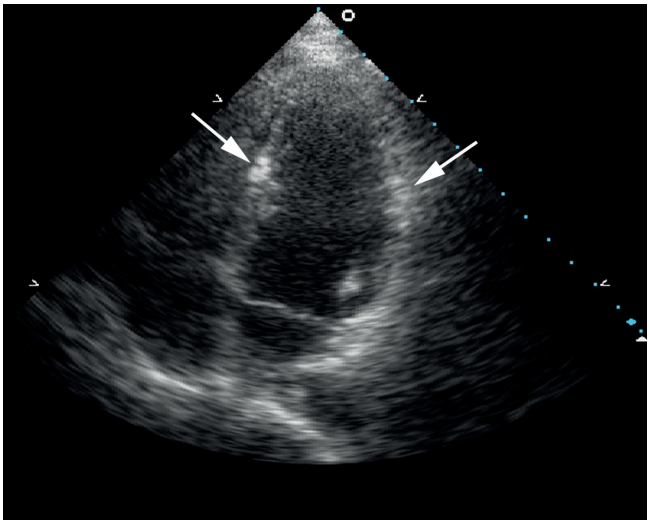


**Figure 2.** Echocardiogram (4-chamber view) of a 23-year-old woman with tuberous sclerosis complex shows 2 focal areas of increased echogenicity; 1 in the interventricular septum (left arrow) and 1 in the left ventricular wall (right arrow).

In the group of patients who had focal areas of abnormal intramyocardial echogenicity, 5 patients had additional echocardiographic abnormalities that were described in the reports as unrelated to the focal areas of abnormal intramyocardial hyperechogenicity. These additional findings (1 per patient) were moderately severe regurgitation of the mitral valve (grade 3), moderately severe stenosis of the aortic valve, absence of a papillary muscle of the anterior mitral valve leaflet, hypokinetic posterior wall of the left ventricle, and hypokinetic interventricular septum (Table 1).

In the group of patients who did not have focal areas of abnormal intramyocardial hyperechogenicity, 6 patients had isolated echocardiographic abnormalities. These findings were moderately severe tricuspid valve regurgitation (grade 2), mild mitral valve regurgitation (grade 1), late systolic mitral valve regurgitation caused by a prolapse of the mitral valve, decreased left ventricle function (ejection fraction, 0.40), hypokinetic and mildly dilated left ventricle, and hypertrophic cardiomyopathy of the left ventricle (Table 1).

## Discussion

There is a discrepancy between the Dutch national TSC guidelines (12;13) and the recommendations for diagnostic evaluation of TSC developed during the Tuberous Sclerosis Consensus Conference in 1998. The Dutch guidelines recommend at least 1 screening echocardiogram in all TSC patients to screen for cardiac rhabdomyomas regardless of the presence of cardiac clinical symptoms, while the international consensus guidelines recommend echocardiography during initial testing only if cardiac symptoms are present or if confirmation of a suspected cardiac lesion is needed for diagnostic purposes (14). Therefore, the purpose of our retrospective study was to determine the frequency of abnormal echocardiographic findings in a relatively large cohort of patients with known TSC who were referred to our cardiology department for screening under the less restrictive Dutch guidelines.

Abnormal cardiac findings were seen in about one third of all patients who were screened. The most common abnormal findings were focal areas of increased intramyocardial echogenicity, which were seen in 16 of 56 patients (29%). Clinical consequence of this finding is not yet known. These focal areas of increased intramyocardial echogenicity might be remnants of rhabdomyomas (that is, hyperechogenic nodules embedded in the ventricles from childhood) because more than half of all infants with TSC show evidence of cardiac rhabdomyomas on echocardiogra-

phy (5-7;15-17). According to the medical literature, rhabdomyomas tend to regress over time (5;6;8-11;15;18;19). Echocardiographic evidence of cardiac rhabdomyomas is reported in about 20% of adult patients who have TSC (6;7). In our study, the patients with focal areas of increased intramyocardial echogenicity were indeed significantly younger than the patients without such focal abnormalities. Furthermore, there appears to be a male predominance among patients with TSC who develop rhabdomyomas (9;15). In our study, there was also a male predominance among patients who showed focal areas of increased intramyocardial echogenicity.

After childhood, patients with TSC who develop cardiac dysfunction suffer mostly from cardiac arrhythmias (14). Although the literature describes an association between cardiac rhabdomyomas and cardiac arrhythmias (15;19-29), cardiac arrhythmias have also been described in TSC patients who have no echocardiographic evidence of rhabdomyomas (14;17;26) and in a patient with only extensive microscopically rhabdomyomatous changes (30). Maybe there is an association between cardiac arrhythmias in TSC and the focal areas of increased intramyocardial echogenicity we found. However, the current study design does not enable us to answer this question.

In conclusion, focal areas of increased intramyocardial echogenicity are commonly seen in patients with TSC. Should a physician, in daily practice, encounter a focal area of increased intramyocardial echogenicity as shown in this article, he or she should remember to look for other features of TSC.

## References

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355(13):1345–1356.
2. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991; 615:125–127.
3. Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of expression in tuberous sclerosis. J Med Genet 1993; 30(1):41–43.
4. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13(12):624–628.
5. Jozwiak S, Kawalec W, Dluzewska J, Daszkowska J, Mirkowicz-Malek M, Michalowicz R. Cardiac tumours in tuberous sclerosis: their incidence and course. Eur J Pediatr 1994; 153(3):155–157.
6. Webb DW, Thomas RD, Osborne JP. Cardiac rhabdomyomas and their association with tuberous sclerosis. Arch Dis Child 1993; 68(3):367–370.
7. Smith HC, Watson GH, Patel RG, Super M. Cardiac rhabdomyomata in tuberous sclerosis: their course and diagnostic value. Arch Dis Child 1989; 64(2):196–200.

8. DiMario FJ, Jr., Diana D, Leopold H, Chameides L. Evolution of cardiac rhabdomyoma in tuberous sclerosis complex. Clin Pediatr 1996; 35(12):615–619.
9. Nir A, Tajik AJ, Freeman WK, Seward JB, Offord KP, Edwards WD et al. Tuberous sclerosis and cardiac rhabdomyoma. Am J Cardiol 1995; 76(5):419–421.
10. Smythe JF, Dyck JD, Smallhorn JF, Freedom RM. Natural history of cardiac rhabdomyoma in infancy and childhood. Am J Cardiol 1990; 66(17):1247–1249.
11. Alkalay AL, Ferry DA, Lin B, Fink BW, Pomerance JJ. Spontaneous regression of cardiac rhabdomyoma in tuberous sclerosis. Clin Pediatr (Phila) 1987; 26(10):532–535.
12. Halley DJJ, Hoff M, Hubbeling A, Lindhout D, Maat-Kievit JA, Mulder J, et al. Wat is Tubereuze Sclerose Complex? 2nd ed. Netherlands: Stichting Tubereuze Sclerose Nederland (STSN), 2004;1–59.
13. Zonnenberg BA, Stroink H, Lequin MH, Oranje AP, van Dorp DB, Siderius EJ. Leidraad voor de medische begeleiding van kinderen met tubereuze sclerose. 1st ed. Netherlands, 1999;1–21.
14. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol 1999; 14(6):401–407.
15. Jozwiak S, Kotulska K, Kasprzyk-Obara J, Domanska-Pakiela D, Tomyn-Drabik M, Roberts P, et al. Clinical and genotype studies of cardiac tumors in 154 patients with tuberous sclerosis complex. Pediatrics 2006; 118(4):e1146-e1151.
16. Bass JL, Breningstall GN, Swaiman KF. Echocardiographic incidence of cardiac rhabdomyoma in tuberous sclerosis. Am J Cardiol 1985; 55(11):1379–1382.
17. Gibbs JL. The heart and tuberous sclerosis. An echocardiographic and electrocardiographic study. Br Heart J 1985; 54(6):596–599.
18. Di Liang C, Ko SF, Huang SC. Echocardiographic evaluation of cardiac rhabdomyoma in infants and children. J Clin Ultrasound 2000; 28(8):381–386.
19. Bosi G, Lintermans JP, Pellegrino PA, Svaluto-Moreolo G, Vliers A. The natural history of cardiac rhabdomyoma with and without tuberous sclerosis. Acta Paediatr 1996; 85(8):928–931.
20. Bar-Cohen Y, Silka MJ, Sklansky MS. Images in cardiovascular medicine. Neonatal tuberous sclerosis and multiple cardiac arrhythmias. Circulation 2007; 115(15):e395-e397.
21. De Wilde H, Benatar A. Cardiac rhabdomyoma with long-term conduction abnormality: progression from pre-excitation to bundle branch block and finally complete heart block. Med Sci Monit 2007; 13(2):CS21-CS23.
22. Isaacs H, Jr. Fetal and neonatal cardiac tumors. Pediatr Cardiol 2004; 25(3):252–273.
23. Emmel M, Brockmeier K, Sreeram N. Rhabdomyoma as accessory pathway: electrophysiologic and morphologic confirmation. Heart 2004; 90(1):43.
24. Krasuski RA, Hesselson AB, Landolfo KP, Ellington KJ, Bashore TM. Cardiac rhabdomyoma in an adult patient presenting with ventricular arrhythmia. Chest 2000; 118(4):1217–1221.
25. Mas C, Penny DJ, Menahem S. Pre-excitation syndrome secondary to cardiac rhabdomyomas in tuberous sclerosis. J Paediatr Child Health 2000; 36(1):84–86.
26. O'Callaghan FJ, Clarke AC, Joffe H, Keeton B, Martin R, Salmon A, et al. Tuberous sclerosis complex and Wolff-Parkinson-White syndrome. Arch Dis Child 1998; 78(2):159–162.
27. Enbergs A, Borggrefe M, Kurlemann G, Fahrenkamp A, Scheld HH, Jehle J, et al. Ventricular tachycardia caused by cardiac rhabdomyoma in a young adult with tuberous sclerosis. Am Heart J 1996; 132(6):1263–1265.
28. Van Hare GF, Phoon CK, Munkenbeck F, Patel CR, Fink DL, Silverman NH. Electrophysiologic study and radiofrequency ablation in patients with intracardiac tumors and accessory pathways: is the tumor the pathway? J Cardiovasc Electrophysiol 1996; 7(12):1204–1210.

29. Mehta AV. Rhabdomyoma and ventricular preexcitation syndrome. A report of two cases and review of literature. Am J Dis Child 1993; 147(6):669–671
30. Gotlieb AI, Chan M, Palmer WH, Huang SN. Ventricular preexcitation syndrome. Accessory left atrio-ventricular connection and rhabdomyomatous myocardial fibers. Arch Pathol Lab Med 1977; 101(9):486–489.

# 3

# Fatty foci in the myocardium in patients with tuberous sclerosis complex: common finding at CT

*Radiology, 2009; 253(2):359-363*

Miraude EAPM Adriaensen, M.D., MSc.
Cornelia M Schaefer-Prokop, M.D., Ph.D.
Debbie AC Duyndam, M.D.
Bernard A Zonnenberg, M.D., Ph.D.
Mathias Prokop, M.D., Ph.D.

## Abstract

**Purpose**: To examine the morphologic characteristics of focal fatty foci in the myocardium of patients with tuberous sclerosis complex (TSC) at computed tomography.

**Materials and Methods**: Institutional review board approval was obtained, and patient informed consent was waived. Fifty-five patients with TSC (mean age, 37 years; range 16–67 years; 22 male patients) who had CT results available that included at least the caudal portions of the heart were included. Fifty-five age- and sex-matched control subjects without TSC were selected from a CT-database. Images were reviewed for the presence of areas of fat attenuation in the depicted portions of the myocardium. Descriptive statistics and the McNemar test for case-control comparisons were used.

**Results**: CT results demonstrated foci of fat attenuation within the myocardium in 35 (64%) of 55 patients with TSC. Foci were well circumscribed and focal and located in the interventricular septum, left ventricle wall, right ventricle wall, and papillary muscles. Size varied between 3 x 1 mm and 62 x 31 mm. Multiple lesions were seen in 19 patients. In the control group, only one (2%) lesion with fat attenuation was found ($P < .001$). Its linear shape and subendocardial location in the left ventricular wall differed from the morphology of fatty foci seen in patients with TSC.

**Conclusion**: Despite incomplete depiction of the heart with CT, the majority of patients with TSC demonstrated well-circumscribed foci of fat attenuation in the myocardium that were not present in age-and sex-matched control subjects. This suggests that such fatty foci may be another characteristic of TSC.

## Introduction

Tuberous sclerosis complex (TSC) is an inheritable multiorgan disease. It is an autosomal-dominant neuro-cutaneous disorder characterized by tumor-like malformations involving many organ systems including brain, kidneys and skin (1). The birth incidence of TSC is approximately one in 5000 to 10000 live births (2). The diagnosis of TSC is made clinically. However, expression and severity of the disease show substantial variation within, as well as, between families (3). The classic diagnostic triad of seizures, mental retardation, and facial angiofibromas occurs in less than half of the patients. Therefore, a clinical scoring system was developed (4) that divides the diagnostic criteria for TSC into major features and minor features. The diagnosis of definite TSC requires the presence of two major features or one major and two minor features. Major features are facial angiofibromas or forehead plaques, shagreen patch, three or more hypomelanotic macules, nontraumatic periungual and ungual fibromas, lymphangioleiomyomatosis, renal angiomyolipoma, cardiac rhabdomyoma, multiple retinal nodular hamartomas, cortical tuber, subependymal nodules, and subependymal giant cell astrocytomas. The list of minor features includes less specific findings and less substantiated signs (4).

Since 1995, our institution has been a national referral center for patients with TSC. A multidisciplinary approach is used according to guidelines published for the Netherlands (5;6): Patients with TSC undergo regular computed tomographic (CT) scanning of the abdomen to monitor renal angiomyolipomas. In daily practice, we noticed focal areas of fat within the myocardium in the caudal portions of the heart at abdominal CT screening.

The purpose of this case-control study was to examine the morphologic characteristics of such focal fatty foci in the myocardium at CT examinations in patients known to have TSC.

## Materials and Methods

### Study Design

A case-control study was performed. The institutional review board at University Medical Center Utrecht approved this retrospective study, and patient informed consent was waived.

We included 55 patients known to have TSC [who had previously been included in an echocardiographic cohort study (7)] who had abdominal CT results available for review in which the caudal portion of the heart was depicted. All patients had definite TSC according to the 1998 diagnostic criteria (4). Mean patient age was 37 years (range, 16–67 years). Thirty-three (60%) of 55 patients with TSC were female.

For a case-control setup, we selected fifty-five control patients without TSC from the CT database of our hospital. Control subjects had similar age- and sex characteristics and had abdominal CT results available for review in which the caudal portion of the heart was depicted. The control subjects were chosen in the following way: A list of all abdominal CT scans performed in our hospital at University Medical Center Utrecht since our radiology department went digital was generated, and male and female patients were sorted according to age (ie, scan date minus date of birth). All patients known to have TSC in our hospital were then excluded from the list. For each TSC case in our study, one of the researchers (M.E.A.P.M.A.) manually selected the first patient with the same sex and a similar age (ie, scan date minus date of birth) as a control subject. The researcher then checked whether the caudal portion of the heart was depicted in the study and, if not, selected the next suitable patient from the list.

We retrospectively reviewed these nongated abdominal CT images for the presence of areas of fat attenuation in the myocardium (see below for scoring procedure).

**CT Data Acquisition**

Patients with TSC underwent abdominal CT either with a single-detector row scanner (AVE, Philips, Best, The Netherlands) or a 16-detector row scanner (Brilliance 16P or MX800 IDT, Philips, Cleveland, OH). With the single-detector row scanner, spiral data acquisition with 5-mm collimation and a 7-mm table feed per rotation was used. Images were reconstructed every 4 mm. With the 16-detector row scanners, a 16 x 1.5mm collimation was applied and images of 5-mm thickness were reconstructed every 4 mm. Tube voltage was 140 kVp on the single-detector row scanner and 120kVp on the 16-detector row scanners. Tube current-time products were fixed at 225mAs on the single-detector row scanner and z-axis tube current modulation (z-DOM, Philips, Cleveland, Ohio) was used on the 16-detector row scanners with a maximum of 250mAs. A precontrast scan of the upper abdomen including the kidneys was followed by a contrast material-enhanced acquisition of

the whole abdomen after injection of 120 mL of contrast material (iopromide, Ultravist 300, Schering, Berlin, Germany) at 3mL/s. No cardiac gating was performed.

Control subjects underwent abdominal CT with a 16-detector row scanner (Brilliance 16P or MX800 IDT, Philips, Cleveland, OH). A 16 x 1.5mm collimation was applied, and images of 5-mm thickness were reconstructed every 4 mm. Tube voltage was 120kVp. Tube current modulation was used with a maximum of 250mAs. A contrast-enhanced acquisition of the whole abdomen was obtained after injection of 120 mL of contrast material (iopromide, Ultravist 300) at 3mL/s. No cardiac gating was performed.

**CT Image Review**

Two researchers (M.E.A.P.M.A, D.A.C.D., with 4 and 9 years of experience, respectively), independently reviewed the depicted caudal part of the heart on the 55 abdominal CT studies in included patients with TSC. The abdominal CT images were reviewed for the presence of well-circumscribed foci with homogeneous fat attenuation (by visually comparing the lesion attenuation with attenuation of the depicted subcutaneous fat) in the myocardium. In the case of a well-circumscribed fatty focus, its maximum perpendicular dimensions in the axial plane were measured, an attenuation measurement (in Hounsfield units) was obtained by using a region of interest at the center of the lesion, and its location within the heart (ie, the interventricular septum, the left ventricular wall, the right ventricular wall, or the papillary muscles) was recorded by one of the researchers (M.E.A.P.M.A). In addition, the two researchers assessed the presence of mass effect of the fatty focus on surrounding structures, signs of invasive behavior, or contrast-enhancing components within the fatty focus by visually looking for signs of displacement of surrounding structures, irregular lesion contours, or enhancing structures when comparing precontrast and postcontrast CT scans. Cases with discrepant ratings by the two researchers were re-evaluated in a consensus session with a third observer (M.P. chest and cardiovascular radiologist with more than 20 years of experience and more than 6 years of experience in interpreting cardiac CT images) to yield a final decision whether or not a patient had fatty foci in the depicted myocardium . In doubtful cases, in which motion artifacts made it too difficult to reach a consensus, a potential lesion was abandoned in order not to overestimate the presence of fatty foci.

The two researchers independently reviewed the depicted part of the heart on the 55 abdominal CT studies in control subjects. The abdominal CT images were

reviewed for the presence of areas of fat attenuation in the myocardium. In the case of a fatty focus, its maximum perpendicular dimensions in the axial plane were measured, an attenuation measurement (in Hounsfield units) was obtained, and its location within the heart was recorded (M.E.A.P.M.A). In addition, mass effect of the fatty focus on surrounding structures, and signs of invasive behavior were noted.

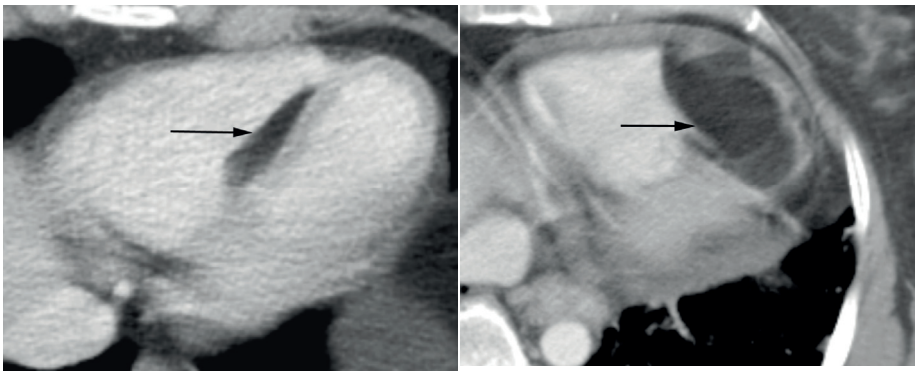
### Data Analysis

Descriptive statistics were used to describe patient characteristics and the number and size of detected lesions. In addition, width-length ratio was calculated from the maximum perpendicular dimensions in the axial plane. We calculated an unweighted kappa statistic to assess interobserver agreement between the two researchers. We used a two-sample t-test to compare means and Chi-square-test to compare proportions within the group of patients with TSC. We used McNemar test for case-control comparison. Analyses were performed with software (Excel for Windows; Microsoft, Redmond, Wash). A P value of less than .05 indicated a significant difference.

## Results

The caudal portion of the heart was depicted in, on average, 13 sections (range, five to 20 sections) of the reviewed abdominal CT images.

Abdominal CT images in patients with TSC showed circumscribed focal areas of fat attenuation in 35 (64%) of 55 patients (Fig 1). Interobserver agreement for detection of circumscribed focal areas of fat attenuation in patients with TSC was high (K = 0.88; 95% confidence interval: 0.76, 1.0). A final decision of whether or not a patient had fatty foci in the depicted myocardium was made three times by the third observer. Discrepancies arose once because the lesion was only seen on the most cranial section and twice because of motion artifacts in the surroundings. In two doubtful cases, in which motion artifacts made it too difficult to reach a consensus, a potential lesion was abandoned.



**a.** **b.**

**Figure 1.** Nongated contrast-enhanced abdominal CT images in patients with TSC show fatty foci in the myocardium. (a) Image in 25-year-old man shows fatty focus in the interventricular septum (arrow). (b) Image in 45-year-old woman shows large fatty focus with mass effect in apex of the left and right ventricle (arrow).

Mean age of patients with such focal fatty foci was 42 years (range, 16–67 years). Mean age of patients with TSC without focal fatty foci was 39 years (range, 18–60 years) and was not significantly different from the mean age of patients with TSC with focal fatty foci (P = .32). There was a tendency towards more foci found in men (17 (77%) of 22) than in women (18 (55%) of 33) (P = .09). The largest fatty focus per patient was located in the interventricular septum in 18 (51%) cases, in the left ventricular wall in nine (26%) cases, in the right ventricular wall in six (17%) cases, and in a papillary muscle in two (6%) cases. The size of the focal fatty foci in the axial plane varied between 3 x 1 mm and 62 x 31 mm. Average length of the largest fatty focus per patient in the axial plane was 20mm (range, 3–62mm). Average width of the largest fatty focus per patient in the axial plane was 6mm (range, 1–31mm). Average width-length ratio was 0.35 (range, 0.12–0.71). The majority of lesions had an ovoid shape (width-length ratio of 0.2–0.8) and a minority of six lesions had a more linear configuration (width-length ratio, < 0.2). Average attenuation of the lesions was –73 HU (range, –139 to –2 HU). Multiple lesions were seen in 19 patients. The average number of lesions in patients with multiple lesions was 2.5 (range, two to four). All lesions were centered in the midwall extending into the subendocardial and/or subepicardial region, depending on their size. No lesion was located exclusively in the subendocardial region. Fatty foci – independent of their size – had no mass effect on surrounding structures with the exception of the larg-

est lesion that filled the apical portion of the heart (Fig 1b). Lesions showed no signs of invasive behavior and no enhancing components.

There was only one (2%) of 55 patients in the control group in whom abdominal CT images showed a thin curvilinear hypoattenuated lesion of fat attenuation in a subendocardial location in the left ventricular wall ($P < .001$) (Fig 2). The size of the lesion was 27 x 2mm. No lesion of such morphology was found in the TSC group. The lesion had no mass effect on surrounding structures and showed no signs of invasive behavior. No other fatty lesions were seen in the control group. Interobserver agreement for detection of circumscribed focal areas of fat attenuation in control subjects was excellent ($K = 1.0$).

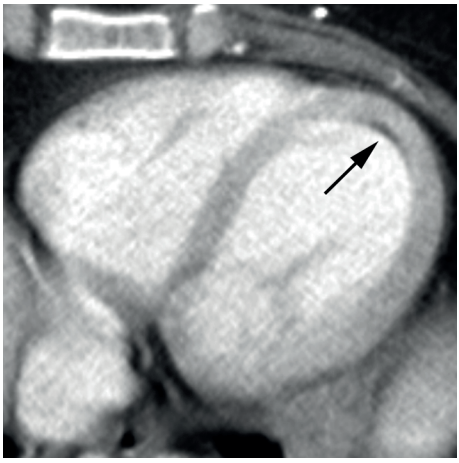


**Figure 2.** CT image in 34-year-old woman shows the only hypoattenuated lesion of fat attenuation (arrow) in our control group. Its curvilinear form and subendocardial location in the left ventricular wall suggest an old infarction.

## Discussion

This article described a high prevalence of well-circumscribed fatty foci in the myocardium of patients with TSC at CT.

Since 1995, our institution has been a national referral center for patients with TSC. During routine evaluation of abdominal CT studies obtained for evaluation of renal angiomyolipomas, we noted abnormal fatty foci in the caudal portions of the heart of these patients. To our knowledge, no systematic prior study on the presence of such findings has been published. In this case-control study, we examined the morphologic characteristics at CT of such focal fatty foci in the myocardium of patients known to have TSC. Despite the fact that we could only evaluate the caudal

regions of the heart and despite the lack of electrocardiographic gating, we found focal fatty foci in the majority of patients with TSC (35 of 55 patients). Only one 34-year-old woman in the control group had a thin curvilinear hypoattenuated lesion in a subendocardial location, which might be suggestive of prior myocardial infarction (8). The fact that there were not more of such findings in the control group may have to do with the relatively young age of our TSC population (and their age and sex-matched control subjects).

We evaluated all well-circumscribed foci with fat attenuation in the myocardium of patients with TSC and found that none showed signs of invasive behavior or had contrast-enhancing components within the areas of fat attenuation. The majority of fatty foci in TSC were located in the interventricular septum and the left ventricular wall. This location differs from intramyocardial fat in the right ventricle that has been described in healthy patients (9) and in patients with arrythmogenic right ventricular dysplasia (ARVD) (10). Patients with ARVD show a more diffuse fat infiltration of the ventricles as opposed to the focal mainly ovoid fatty foci seen in TSC as described in our study (10;11). We did not observe any enhancing components in the fatty foci in TSC as opposed to the marked enhancement seen in primary cardiac hemangioma, a lesion that may contain fat (12–14). Except for the largest lesion of 62 x 31 mm, no mass effect on surrounding structures could be noted. This differs from the mass effect and invasive behavior that would be typical for liposarcoma (14;15).

The well-circumscribed fatty foci in the myocardium of patients with TSC differed in morphology from the focus seen in our control group and from most foci described in the literature (9–14). Fatty foci in TSC-patients appear to have unique CT characteristics with respect to location, attenuation, focality, absence of enhancement, and absence of invasive behavior that most closely resembles that of lipomas seen in other parts of the body. True intramyocardial lipomas have been described in the literature (16). Usually, these lipomas are small, have an irregular contour, and have a capsule (16). The association of multiple intramyocardial lipomas and TSC has already been reported in three patients in 1978 (16). Whether the fatty foci we observed histologically resemble or indeed represent lipomas remains open since we do not have histopathologic proof.

It has also been described that perivascular epithelioid cells (PECs) seen in patients with pulmonary lymphangioleiomyomatosis (LAM) have the same genetic and immunohistochemical characteristics as those in angiomyolipomas, which often accompany LAM (17). LAM and angiomyolipomas are both major diagnostic features of TSC. These PECs apparently have the ability to differentiate into fat and

vessels, as well as smooth muscle (17). Hypothetically, the intramyocardial fat seen in patients with TSC might have differentiated from PECs as well.

Because none of the patients in our study has died we do not have a histopathologic correlation of our findings. As a consequence, the origin of the intramyocardial fatty foci seen in the majority of patients with TSC in our study is still unknown. However, the unique CT appearance of these intramyocardial fatty foci and the high prevalence of these foci in patients with TSC might help to identify patients suspected of having TSC.

A limitation of our retrospective study was that only the caudal part of the heart was available for review on abdominal CT images. Furthermore, the CT studies were not gated, thus cardiac motion may have obscured some small fatty foci. Nevertheless, we were still able to demonstrate this unsuspected finding in the myocardium of a large number of patients with TSC. Despite similar scanning technique and similar limitations, such findings were lacking in the control group. As a result, the true number of lesions that could be detected by gated CT scanning of the whole heart in patients with TSC is likely to be larger.

Because characteristic well-circumscribed foci of fat attenuation were found in the majority of patients with TSC and not in the control group, such fatty foci may help identify patients suspected of having the disease. Adding fatty foci in the myocardium to the list of major features of tuberous sclerosis complex may be considered in the future.

## References

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355(13):1345-1356.
2. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991; 615:125-127.
3. Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of expression in tuberous sclerosis. J Med Genet 1993; 30(1):41-43.
4. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13(12):624-628.
5. Halley DJJ, Hoff M, Hubbeling A, Lindhout D, Maat-Kievit JA, Mulder J et al. Wat is Tubereuze Sclerose Complex? 2nd ed. Zeist, the Netherlands: Stichting Tubereuze Sclerose Nederland (STSN), 2004;1-59
6. Zonnenberg BA, Stroink H, Lequin MH, Oranje AP, van Dorp DB, Siderius EJ et al. Leidraad voor de medische begeleiding van kinderen met tubereuze sclerose. 1st ed. Velp, the Netherlands, 1999;1-21
7. Brouha MEE, Cramer MJM, Zonnenberg BA, Hofstra L, Doevendans PA. If you survive tuberous sclerosis, do not be scared of the cardiac scar [abstr]. Eur Heart J 2004;25(suppl):614.

8. Zafar HM, Litt HI, Torigian DA. CT imaging features and frequency of left ventricular myocardial fat in patients with CT findings of chronic left ventricular myocardial infarction. Clin Radiol 2008; 63(3):256-262.
9. Tansey DK, Aly Z, Sheppard MN. Fat in the right ventricle of the normal heart. Histopathology 2005; 46(1):98-104.
10. Kayser HW, van der Wall EE, Sivananthan MU, Plein S, Bloomer TN, de Roos A. Diagnosis of arrhythmogenic right ventricular dysplasia: a review. Radiographics 2002; 22(3):639-648.
11. Tandri H, Macedo R, Calkins H, Marcus F, Cannom D, Scheinman M et al. Role of magnetic resonance imaging in arrhythmogenic right ventricular dysplasia: insights from the North American arrhythmogenic right ventricular dysplasia (ARVD/C) study. Am Heart J 2008; 155(1):147-153.
12. Sparrow PJ, Kurian JB, Jones TR, Sivananthan MU. MR imaging of cardiac tumors. Radiographics 2005; 25(5):1255-1276.
13. Grebenc ML, Rosado de Christenson ML, Burke AP, Green CE, Galvin JR. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics 2000; 20(4):1073-1103.
14. Araoz PA, Mulvagh SL, Tazelaar HD, Julsrud PR, Breen JF. CT and MR imaging of benign primary cardiac neoplasms with echocardiographic correlation. Radiographics 2000; 20(5):1303-1319.
15. Gaerte SC, Meyer CA, Winer-Muram HT, Tarver RD, Conces DJ, Jr. Fat-containing lesions of the chest. Radiographics 2002; 22 Spec No:S61-S78.
16. McAllister HA, Fenoglio JJ. Tumors of the cardiovascular system. In: Armed Forces Institute of Pathology, editor. Atlas of Tumor Pathology. Washington D.C.: Armed Forces Institute of Pathology, 1978: 40-46.
17. Bonetti F, Pea M, Martignoni G, Zamboni G, Manfrin E, Colombari R et al. The perivascular epithelioid cell and related lesions. Advances in Anatomic Pathol 1997; 4:343-358.

# 4

# Focal fatty areas in the myocardium of patients with tuberous sclerosis complex: a unique finding

*Journal of Thoracic Imaging, 2011; 26(1):W12-W13*

Miraude EAPM Adriaensen, M.D., MSc.
Harm HH Feringa, M.D., Ph.D.
Cornelia M Schaefer-Prokop, M.D., Ph.D.
Sandra AP Cornelissen, M.D., MSc.
Bernard A Zonnenberg, M.D., Ph.D.
Mathias Prokop, M.D., Ph.D.

## Abstract

With this collection of computed tomography and magnetic resonance images, we illustrate a recently described novel finding in the myocardium of patients with tuberous sclerosis complex.

## Introduction

With this collection of computed tomography (CT) and magnetic resonance (MR) images, we illustrate a recently described finding in the myocardium of patients with tuberous sclerosis complex (TSC). TSC is an autosomal-dominant neurocutaneous disorder characterized by tumor-like malformations involving many organ systems including the brain (cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas), the lungs (lymphangioleiomyomatosis), the kidneys (angiomyolipomas) and the skin (facial angiofibromas or forehead plaques, shagreen patches, and hypomelanotic macules) (1).

## Case report

Within the field of cardiology, patients with TSC can present at a fetal or pediatric age due to the development of cardiac rhabdomyomas which tend to regress over time. After childhood, patients with TSC who develop cardiac dysfunction suffer mostly from cardiac arrhythmias (2). In Figure 1 we show two different patients with TSC with focal circumscribed hypodense areas within the myocardium depicted on abdominal CT scans performed to monitor their renal angiomyolipomas. On MR, these fatty foci show the signal intensity of fat (Fig. 2).

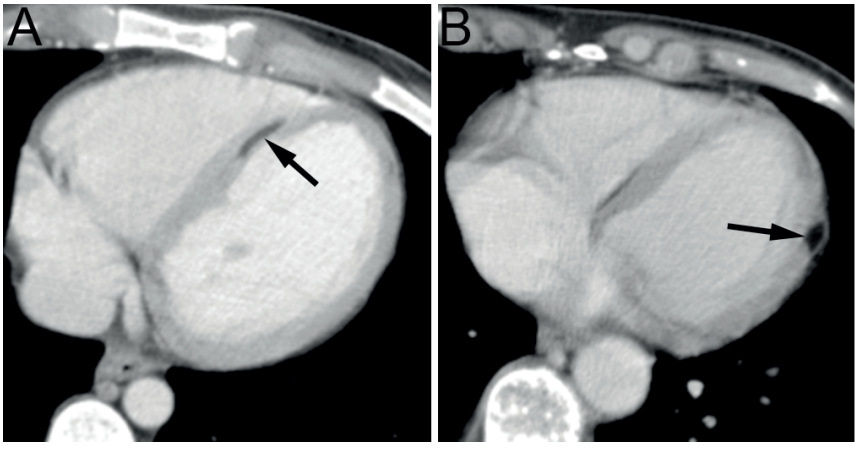



**Figure 1.** Fatty foci in the myocardium demonstrated on non-gated contrast-enhanced abdominal CT scans in patients with TSC. (A) Fatty focus in the interventricular septum (arrow) in a 25-year-old male patient. (B) Fatty focus in the left ventricular wall (arrow) in a 59-year-old female patient.

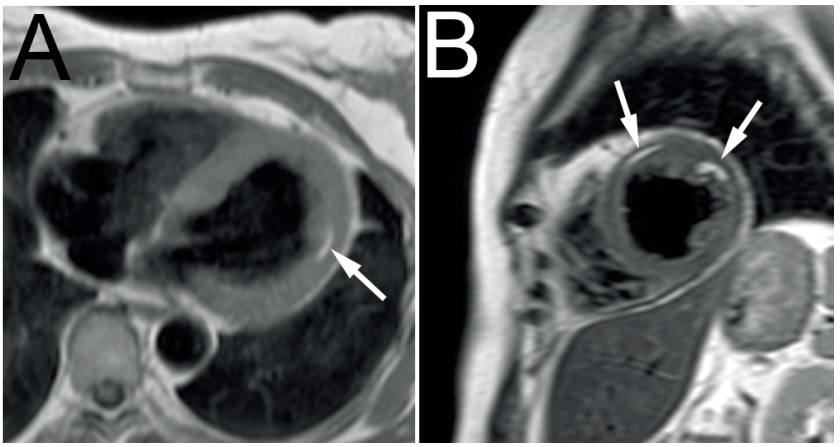



**Figure 2.** Fatty foci in the myocardium demonstrated on MRI in a 49-year-old female patient with TSC. (A) Transverse dark-blood T1-weighted TSE image. Arrow points at fatty focus in the left ventricular wall. (B) Short axis dark-blood T2-weighted TSE image. Arrows points at fatty foci in the left ventricular wall. TSE indicates Turbo Spin Echo.

## Discussion

In comparison with the known causes of fat in the myocardium (ie, epicardial fat deposits, old myocardial infarctions, arrhythmogenic right ventricular dysplasia, normal right ventricular fat, hemangiomas, and liposarcomas), the fatty foci in patients with TSC seem to have unique characteristics consisting of a combination of focality, well-circumscribed form, location into the mid myocardium, pure fat density, absence of enhancement, and absence of invasive behavior (3). In a recently published case-control study, the majority of patients with TSC showed these well-circumscribed foci of fat density in the myocardium on abdominal CT scans, which were not found in an age-matched and sex-matched control group without TSC (3). To our knowledge, no MR images of these characteristic fatty foci in TSC have been published yet. On echocardiography, these fatty foci can be seen as areas of increased echogenicity (4). Therefore, if in daily practice one encounters these type of fatty foci in the myocardium on cardiac CT, cardiac MR, or echocardiography, one should remember to look for other features of TSC.

## References

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med*. 2006;355:1345-1356.
2. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *J Child Neurol*. 1999;14:401-407.
3. Adriaensen MEAPM, Schaefer-Prokop CM, Duyndam DA, et al. Fatty Foci in the Myocardium in Patients with Tuberous Sclerosis Complex: Common Finding at CT. *Radiology*. 2009;253(2):359-363
4. Adriaensen MEAPM, Cramer MJM, Brouha MEE, et al. Findings in screening echocardiography in patients with tuberous sclerosis complex. *Tex Heart Inst J*. 2010;37(3):280-283

# 5

# Mature fat cells in the myocardium of patients with tuberous sclerosis complex

*Journal of Clinical Pathology, 2011; January 7. [Epub ahead of print]*

Miraude EAPM Adriaensen, M.D., MSc.
Matthijs FM van Oosterhout, M.D., Ph.D.
Harm HH Feringa, M.D., Ph.D.
Cornelia M Schaefer-Prokop, M.D., Ph.D.
Bernard A Zonnenberg, M.D., Ph.D.
Mathias Prokop, M.D., Ph.D.

## Abstract

**Aim:** Routine abdominal CT scans in patients with tuberous sclerosis complex (TSC) showed characteristic fatty foci in the depicted caudal portions of the myocardium. Purpose of this study was to investigate if areas of abnormal myocardium in patients with TSC could also be found in post mortem specimen.
**Methods:** A retrospective search of our histopathology database was performed to identify specimens of the heart of patients with TSC. Institutional review board approval was obtained, and patient informed consent was waived. Four specimens were included (mean age, 44years; range 32–68 years; 2 female).
**Results:** Two specimens (50%) of the heart showed areas of mature fat cells in the myocardium, without associated inflammation, without associated fibrosis, without entrapped myocardial cells, and without a capsule.
**Conclusion:** Post mortem specimens of the heart of patients with tuberous sclerosis complex showed areas of mature fat cells in the myocardium which seem to be unique for tuberous sclerosis complex.

## Introduction

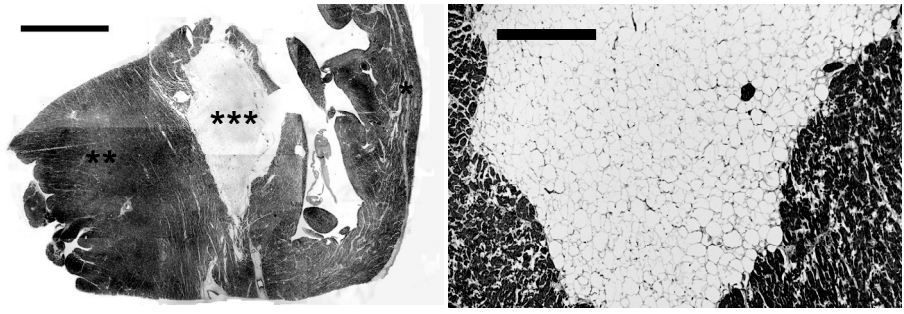
Tuberous sclerosis complex (TSC) is an inheritable multiorgan disease. It is an autosomal-dominant neuro-cutaneous disorder characterized by tumor-like malformations involving many organ systems including brain, lungs, heart, kidneys and skin (1). Since 1995, our institution is a national referral center for patients with TSC. Patients are extensively evaluated by radiological imaging. Routine abdominal CT scans for the evaluation of renal angiomyolipomas had shown well-circumscribed, non-enhancing, focal areas of fat density in the myocardium of patients with TSC in the depicted caudal portions of the heart. In a case-control study, the majority of patients with TSC showed these well-circumscribed foci of fat density in the myocardium which were not found in an age- and sex-matched control group without TSC (2). The purpose of this study was to investigate if areas of abnormal myocardium in patients with TSC could also be found in post mortem specimen.

## Methods

A search of the histopathology database of University Medical Center Utrecht was performed. The institutional review board at University Medical Center Utrecht approved this retrospective study, and patient informed consent was waived. Post mortem specimens of the heart were included if the patient had been diagnosed with definite TSC according to the 1998 revised diagnostic criteria for TSC(3), and the specimen was available for review. Four post mortem specimens of the heart fulfilled these inclusion criteria and were included in this study. Mean patient age was 44 years (range, 32–68 years). Two (50%) of four patients were female. Our pathologist subspecialized in cardiac pathology (M.F.M.O) reviewed the post mortem specimens to look specifically for focal myocardial abnormalities that could correlate with the imaging findings on CT of well-circumscribed, non-enhancing, focal areas of fat density in the myocardium. Routine H&E stained sections were available for review as well as Elastica van Giesson and modified Azan stained sections to detect any associated fibrosis.

## Results

Two specimens (50%) out of four specimens of the heart showed no abnormalities in the myocardium. The two other specimens (50%) did show abnormalities in the myocardium. One specimen of the heart belonging to a 68-year-old, female, patient with TSC who died from renal failure as she refused dialysis, showed multiple areas of mature fat in the myocardium without any associated inflammation, without entrapped myocardial cells, and without a capsule. Circumscribed areas of mature fat cells were seen in the interventricular septum and in the left ventricular free wall (Fig. 1). Modified Azan and Elastica van Giesson stained sections showed that there was also no associated fibrosis surrounding the areas of mature fat. A similar area of mature fat was seen in the left ventricular free wall of the specimen of the heart belonging to a 32-year-old, male, TSC-patient who died most likely from either an epileptic fit or a cardiac arrhythmia. Size of the areas of mature fat in the myocardium of the specimens ranged from 3 mm to 10 mm.




**1a.** **1b.**

**Figure 1.**Histopathology. Multiple foci of mature fat cells in the myocardium of a 68-year-old, female patient with tuberous sclerosis complex who died from renal failure as she refused dialysis.
**Figure 1a** H&E stained specimen showing a focal area of mature fat within the myocardium of the interventricular septum. * = right ventrical free wall; ** = interventricular septum; *** = focal area of mature fat within the myocardium. Bar equals 0.5 centimeter.
**Figure 1b** H&E stained specimen showing the individual mature fat cells within the myocardium. Bar equals 300 micrometer.

## Discussion

Routine abdominal CT scans for the evaluation of renal angiomyolipomas in patients with tuberous sclerosis complex had shown fatty foci in the depicted caudal portions of the heart (2). These fatty foci appear to have unique CT characteristics consisting of a combination of focality, well-circumscribed form, location into the mid myocardium, pure fat density, absence of enhancement, and absence of invasive behaviour (2). Purpose of this study was to investigate if areas of abnormal myocardium in patients with TSC could also be found in post mortem specimens. Indeed, two specimens (50%) out of four included specimens of the heart did show areas of mature fat cells in the myocardium.

The areas of mature fat cells in the myocardium of patients with TSC we described in this study differ from other fat deposits described in the heart. The mature fat cells were located intramyocardial as opposed to the epicardial localization of frequently seen epicardial fat and of cardiac adiposity (4). The fat cells were located in the interventricular septum and the left ventricular wall as opposed to the exclusive or predominant localization of fat cells in the right ventricle in patients with normal intramyocardial fat of the right ventricle and in patients with arrythmogenic right ventricular dysplasia (ARVD) (5–7). We observed no findings of associated fibrosis as opposed to patients with fibrofatty replacement in ARVD and in inherited myopathies (6;8;9). Histopathology did not show a capsule or entrapped myocardial cells as opposed to a definite capsule and invariably entrapped myocardial cells in true intramyocardial lipomas (10). We did not see any mass effect on surrounding structures or signs of invasive behaviour as opposed to the mass effect and invasive behaviour that would be typical for liposarcoma (11;12).

The association of multiple intramyocardial lipomas and TSC has been reported in three patients in 1978 (10). However the areas of mature fat cells in the myocardium reported in our study did not show a capsule or any entrapped myocardial cells.

To conclude histopathology in patients with tuberous sclerosis complex showed multiple areas of mature fat cells in the myocardium without associated inflammation, without associated fibrosis, without entrapped myocardial cells, and without a capsule which to the best of our knowledge have not been published before and seem to be unique for tuberous sclerosis complex.

## References


1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355(13): 1345–1356.
2. Adriaensen ME, Schaefer-Prokop CM, Duyndam DA, Zonnenberg BA, Prokop M. Fatty Foci in the Myocardium in Patients with Tuberous Sclerosis Complex: Common Finding at CT. Radiology 2009;253(2):359–363.
3. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998;13(12):624–628.
4. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BD, Woomert CA et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. Am J Cardiol 2008;102(6):767–771.
5. Tansey DK, Aly Z, Sheppard MN. Fat in the right ventricle of the normal heart. Histopathology 2005;46(1):98–104.
6. Fletcher A, Ho SY, McCarthy KP, Sheppard MN. Spectrum of pathological changes in both ventricles of patients dying suddenly with arrhythmogenic right ventricular dysplasia. Relation of changes to age. Histopathology 2006;48(4):445–452.
7. Kayser HW, van der Wall EE, Sivananthan MU, Plein S, Bloomer TN, de Roos A. Diagnosis of arrhythmogenic right ventricular dysplasia: a review. Radiographics 2002;22(3):639–648.
8. Nguyen HH, Wolfe JT, III, Holmes DR, Jr., Edwards WD. Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. J Am Coll Cardiol 1988;11(3):662–671.
9. Muraoka H, Negoro N, Terasaki F, Nakakoji T, Kojima S, Hoshiga M et al. Re-entry circuit in ventricular tachycardia due to focal fatty-fibrosis in a patient with myotonic dystrophy. Intern Med 2005;44(2):129–135.
10. McAllister HA, Fenoglio JJ. Tumors of the cardiovascular system. In: Armed Forces Institute of Pathology, editor. Atlas of Tumor Pathology. Washington D.C.: Armed Forces Institute of Pathology, 1978:40–46.
11. Gaerte SC, Meyer CA, Winer-Muram HT, Tarver RD, Conces DJ, Jr. Fat-containing lesions of the chest. Radiographics 2002;22:S61-S78.
12. Neragi-Miandoab S, Kim J, Vlahakes GJ. Malignant tumours of the heart: a review of tumour type, diagnosis and therapy. Clin Oncol (R Coll Radiol ) 2007;19(10):748–756.

# 6

# Radiologic evidence of pulmonary lymphangioleiomyomatosis in female and male patients with tuberous sclerosis complex

*Submitted*

Miraude EAPM Adriaensen, M.D., MSc.
Cornelia M Schaefer-Prokop, M.D., Ph.D.
Debbie AC Duyndam, M.D.
Bernard A Zonnenberg, M.D., Ph.D.
Mathias Prokop, M.D., Ph.D.

*Presented at the 92nd Scientific Assembly and Annual Meeting of the Radiological Society of North America, 2006.*

## Abstract

**Objective:** To determine the gender-specific prevalence of pulmonary cysts typical for lymphangioleiomyomatosis (LAM) in adult patients with known tuberous sclerosis complex (TSC).

**Materials and methods:** Retrospective cross-sectional study in a cohort of 206 adult TSC-patients was performed. Institutional review board approval was obtained, and patient informed consent was waived. Patients had routinely undergone abdominal CT scanning between 1996 and 2006. All 186 patients (mean age, 38 years; range 19-72 years; 91 (49%) male patients) in whom at least the lung bases were depicted on CT were included. Images were reviewed for the presence of pulmonary thin-walled cysts. Descriptive statistics, two sample t-test to compare means, and $X^2$-test to compare proportions were applied.

**Results:** CT demonstrated pulmonary thin-walled cysts in the lung bases in 52 (28%) of 186 patients. Size varied from 2mm in diameter to more than 2cm. Pulmonary cysts were detected in 40 (42%) of 95 female patients and in 12 (13%) of 91 male patients ($P<0.001$). In general, cysts were larger and more numerous in women than in men. Only minimal cystic changes were found in 4 women and 2 men, moderate cystic changes were seen in 3 women and 7 men, but considerable cystic changes were seen almost exclusively in women (33 women versus 3 men).

**Conclusions:** CT demonstrated thin-walled pulmonary cysts in the lung bases in 28% of 186 included patients with tuberous sclerosis complex. Females were more affected than males.

## Introduction

Tuberous sclerosis complex (TSC) is an inheritable multiorgan hamartosis. It is an autosomal-dominant neuro-cutaneous disorder characterized by tumor-like malformations involving many organ systems including brain, kidneys and skin (1). The disease is rare with a birth incidence of approximately one in 5,000 to 10,000 live births (2). The diagnosis of TSC is made clinically. However, the expression and the severity of the disease show substantial variation within as well as between families (3). Therefore, a clinical scoring system was developed (4) that divides the diagnostic criteria for TSC into major features and minor features. Lymphangioleiomyomatosis (LAM) is one of the major features (4).

Pulmonary lymphangioleiomyomatosis (LAM) is mainly characterized by diffusely distributed pulmonary thin-walled cysts. The incidence of LAM in the general population is not known but it is reported almost exclusively in women of reproductive age (5). The clinical presentation of LAM includes recurrent pneumothoraces, recurrent chylous pleural effusions, and gradually progressive diffuse interstitial lung disease (6). Histopathology shows widespread proliferation of smooth muscle-like cells around small airways, alveolar walls, lymphatic vessels, and blood vessels (7;8). CT findings are pathognomonic and consists of multiple, thin-walled cysts of varying size, diffusely distributed throughout the lungs including the costophrenic angles with normal intervening lung parenchyma (6;9).

It is known that LAM occurs more frequently in patients with TSC but reported prevalence varies widely: early reports mention a prevalence of between approximately 1% and 2.3% (6;9-13). More recent studies demonstrate a much higher prevalence in female patients: between 26% (14) and 34% (15). In male patients the reported prevalence is very low (15) but multiple case reports have described findings of LAM in males (10;16-20).

Our institution is a large national referral center for patients with TSC. Patients are screened and monitored for various manifestations of the disease (21;22). Abdominal CT is used for detection and monitoring of renal angiomyolipomas. On these scans we noted a high prevalence of thin-walled cysts in the depicted basal portions of the lungs, even in male patients. Because LAM is known to be a diffuse disease with no cranio-caudal predominance (5;6;9), we decided to study the prevalence of such cysts in our cohort.

The purpose of this retrospective cross-sectional cohort study was to determine the gender-specific prevalence of thin-walled cysts in the lung parenchyma of adult patients with known tuberous sclerosis complex (TSC).

## Materials and methods

### Study design

Our institution is a nationwide tertiary referral center for TSC since 1995. In 2006, our patient population comprised 206 adult patients with TSC and 40 pediatric patients with TSC. In this cross-sectional study we retrospectively reviewed the most recent CT scan of the lung bases for radiologic evidence of LAM i.e. pulmonary thin-walled cysts. Our institutional review board approved this retrospective study, and patient informed consent was waived. Patients were included if they had definite TSC (4), were older than 21 years on the 1$^{st}$ of March 2006, and had a CT scan available for review in which at least the lung bases were depicted. These criteria were fulfilled by 186 (90%) of 206 adult patients with definite TSC. CT scans dated from August 1996 to February 2006. The available CT scan was a CT scan of the abdomen in 169 patients, and a combined CT scan of the thorax and abdomen in 17 patients. Two researchers (with 5 and 10 years of experience within the field of radiology) independently reviewed the CT scans for radiologic evidence of LAM. Cases with discrepant ratings by the two researchers were reevaluated in a consensus session and a final decision was made. The CT scans were reviewed for the presence of thin-walled cysts in the lung bases. The severity of cystic parenchymal changes was scored on the base of the numbers of cysts as minimal cystic changes (less than four cysts), moderate cystic changes (between four and ten cysts), and considerable cystic changes (more than ten cysts).

We also documented if evidence of LAM was mentioned in the original dictated report.

### Imaging technique

Between 1996 and 2006, subjects underwent either computed tomography of the abdomen or computed tomography of the thorax and the abdomen on a single detector row scanner (AVE, Philips, Best, The Netherlands), a 16-detector row scanner (Brilliance 16P or MX800 IDT, Philips, Cleveland, OH) or a 40-detector row scan-

ner (Brilliance 40, Philips, Cleveland, OH). A precontrast scan of the upper abdomen including the kidneys was followed by a contrast-enhanced scan of the whole abdomen or the whole torso after injection of contrast material (Iopromide, Ultravist 300, Schering, Germany).

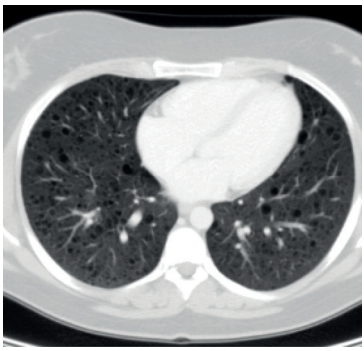
### Data analysis

Descriptive statistics were used to describe patient characteristics, and the number and size of detected lesions. We used two sample t-test to compare means and $X^2$-test to compare proportions between the sexes. Analyses were performed with Excel for Windows (Microsoft Corporation, Redmond, WA, USA).

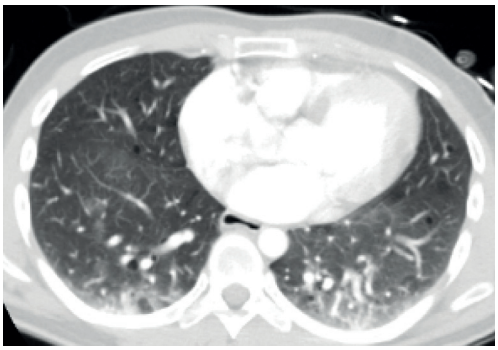
## Results

Of our cohort of 206 adult patients with definite TSC (101 men; 49%), 186 (90%) patients were included this study. Of the 186 included patients, 91 (49%) patients were male. Mean age of included patients at the scan date was 38 years (range 19 to 72 years). Gender specific mean age at the scan date was 38 years in women and 37 years in men (P=0.86).

CT demonstrated pulmonary thin-walled cysts in the lung bases in 52 (28%) out of 186 patients (Fig. 1). The majority of pulmonary thin-walled cysts was detected in women (40 (42%) out of 95 female patients). However pulmonary thin-walled cysts were also detected in men (12 (13%) out of 91 male patients, P<0.001). Gender specific mean age at the scan date in patients with pulmonary thin-walled cysts was 42 years in women and 40 years in men (P=0.64).



**1a.**



**1b.**

**Figure 1.** Two examples of CT findings of thin-walled pulmonary cysts in the lung bases consistent with lymphangioleiomyomatosis in patients with tuberous sclerosis complex
**Figure 1a.** Lung bases of a 29 year old female patient with tuberous sclerosis complex with radiologic evidence of lymphangioleiomyomatosis.
**Figure 1b.** Lung bases of a 33 year old male patient with tuberous sclerosis complex with radiologic evidence of lymphangioleiomyomatosis.

Number of cysts within a single patient varied from just a few to countless (Table 1). Following a qualitative classification of minimal (less than 4 cysts), moderate (between 4 and 10 cysts) and considerable (more than 10 cysts) cystic parenchymal changes we found the following:

- For minimal cystic changes we found an overall prevalence of 3% (4 women and 2 men) with an average age of 32 years, gender specific prevalence was 4% and 2%, respectively;
- For moderate cystic changes we found an overall prevalence of 5% (3 women and 7 men) with an average age of 44 years, gender specific prevalence was 3% and 8%, respectively;
- For considerable cystic changes we found an overall prevalence of 19% (33 women and 3 men) with an average age of 42 years, gender specific prevalence was 35% and 3%, respectively.

Size of cysts varied from 2 mm in diameter to 12 cm. In general cysts tended to be larger and more numerous in women than in men.

Evidence of LAM in the lung parenchyma was mentioned in the original report in 18 (35%) out of the 52 patients with radiologic evidence of LAM.

**Table 1.** Gender specific and overall number of pulmonary thin-walled cysts per individual detected in male and female patients with tuberous sclerosis complex

| | No. of Affected Individuals (percentage per column) | | |
|---|---|---|---|
| No. of cysts per patient | Men (n = 91) | Women (n = 95) | Total (n = 186) |
| 1-3 | 2 (2%) | 4 (4%) | 6 (3%) |
| 4-10 | 7 (8%) | 3 (3%) | 10 (5%) |
| > 10 | 3 (3%) | 33 (35%) | 36 (19%) |
| Any | 12 (13%) | 40 (42%) | 52 (28%) |

No. = absolute number; n = absolute number of patients per column included in our study; % = affected individuals as a percentage of all the patients per column included in our study; > = more than

## Discussion

In this study we investigated the gender-specific prevalence of pulmonary cysts typical for lymphangioleiomyomatosis (LAM) in adult patients with known tuberous sclerosis complex (TSC).

CT findings characteristic of LAM consists of multiple, thin-walled cysts of varying size, diffusely distributed throughout the lungs with normal intervening lung parenchyma (6;9).

The morphologic finding of cystic parenchymal changes, as seen in LAM or TSC, include a number of other diagnosis that demonstrate with cystic or cavitating parenchymal changes but usually can be differentiated either on the basis of morphological characteristics of the cysts, the distribution of disease, a different history and/or different symptoms.

The differential diagnosis of cystic diffuse lung diseases includes LAM (disseminated thin-walled cysts, evenly distributed throughout the lungs), histiocystosis (cysts of varying size in upper 2/3 of the lungs, and sparing of costophrenic angles), emphysema (usually imperceptible walls), neurofibromatosis (predominantly apical) and lymphoid interstitial pneumonia (associated with diffuse ground-glass opacities and rarely with nodules, mainly associated with other immunologic diseases).

Our study demonstrated pulmonary thin-walled cysts with intervening normal lung parenchyma in the lung bases in 28% of adult TSC-patients. Gender specific prevalence was 42% in female and 13% in male TSC-patients. Our prevalence is considerably higher than previously reported in the literature (6;9-15). Moreover, the prevalence in male TSC-patients is higher than previously reported (11;15).

Although it is known that LAM occurs more frequently in patients with TSC, it was previously assumed that LAM occurs in approximately 1% of TSC-patients (6;9-12). However, Hancock *et al* already noted that no study so far had screened TSC patients for LAM so the true prevalence of LAM would possibly be higher than estimated from symptomatic patients (18).

Castro *et al* described nine female patients with evidence of LAM out of 388 patients with TSC seen at the Mayo Clinic in the period from 1948 to 1991, giving an overall prevalence of 2.3% (13). More recently, Costello *et al* described 20 female patients with evidence of LAM out of 78 female patients with definite TSC seen at the Mayo Clinic from 1977 to 1998, giving a gender specific prevalence of 26% in female patients with definite TSC (14). Moss *et al* screened 48 patients with TSC and no prior history of LAM (15). Thirteen out of 38 female TSC-patients exhibited pulmonary parenchymal cysts consistent with the diagnosis of LAM, giving a gender specific prevalence of 34%. Evidence of LAM was not observed in the ten screened male TSC-patients.

Review of the English literature revealed a couple of articles suggesting or reporting evidence of LAM in a total of 13 male TSC-patients (10;16-20;23;24). The earliest dated from 1951 (20), the most recent one dated from 2005 (16), they reported on male TSC-patients in the age range from 6 months (18) to 64 years old (20). Some of the articles based their descriptions on histological proof (10;16-19). Noteworthy is that two of the articles mentioned pneumothorax (18;23) and one chylothorax (24) i.e. the known complications of LAM in women.

In general we found more and larger cysts in women than in men. Whether also the complication rate of recurrent pneumothoraces, recurrent chylothoraces or respiratory failure with the need for transplantation is lower in men than in women has to remain open but can be suspected given the lack of evidence for that in the literature. It is noteworthy that the mean age of our female and male study-group was comparable indicating that the more extensive disease seen in females was gender and not age specific.

The main limitation of this study is that we did not have a CT of the thorax available for every patient. Nonetheless, as radiologic evidence of LAM occurs more frequently than previously reported in female and male patients with TSC, it is important for radiologists who report CT scans of TSC patients to look for thin-walled cysts in the lung parenchyma and to identify TSC patients who are at risk of pulmonary

symptoms. Vice versa clinicians should be advised to look for other possible features of TSC when imaging demonstrates evidence of LAM, although LAM also occurs as a sporadic, non inheritable pulmonary disorder in patients without TSC (5).

To conclude CT more frequently demonstrated radiologic evidence of lymphangioleiomyomatosis in female and male patients with tuberous sclerosis complex than previously described. Overall prevalence was 28 percent with a gender specific prevalence of 42 percent in women and 13 percent in men.

## References


1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355(13):1345-1356.
2. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991; 615:125-127.
3. Northrup H, Wheless JW, Bertin TK, et al. Variability of expression in tuberous sclerosis. J Med Genet 1993; 30(1):41-43.
4. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13(12):624-628.
5. Abbott GF, Rosado-de-Christenson ML, Frazier AA, et al. From the archives of the AFIP: lymphangioleiomyomatosis: radiologic-pathologic correlation. Radiographics 2005; 25(3):803-828.
6. Daehnert W. Chest Disorders. In: Daehnert W, editor. Radiology Review Manual. Philadelphia: Lippincott Williams & Wilkins, 2003: 501.
7. Corrin B, Liebow AA, Friedman PJ. Pulmonary lymphangiomyomatosis. A review. Am J Pathol 1975; 79(2):348-382.
8. Pacheco-Rodriguez G, Kristof AS, Stevens LA, et al. Giles F. Filley Lecture. Genetics and gene expression in lymphangioleiomyomatosis. Chest 2002; 121(3 Suppl):56S-60S.
9. Schaefer-Prokop C, Prokop M. Lungs and Tracheobronchial System. In: Prokop M, Galanski M, editors. Spiral and Multislice Computed Tomography of the Body. Stuttgart: Thieme, 2003: 364-365.
10. Dwyer JM, Hickie JB, Garvan J. Pulmonary tuberous sclerosis. Report of three patients and a review of the literature. Q J Med 1971; 40(157):115-125.
11. Hancock E, Osborne J. Lymphangioleiomyomatosis: a review of the literature. Respir Med 2002; 96(1):1-6.
12. Jao J, Gilbert S, Messer R. Lymphangiomyoma and tuberous sclerosis. Cancer 1972; 29(5):1188-1192.
13. Castro M, Shepherd CW, Gomez MR, et al. Pulmonary tuberous sclerosis. Chest 1995; 107(1):189-195.
14. Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. Mayo Clin Proc 2000; 75(6):591-594.
15. Moss J, Avila NA, Barnes PM, et al. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med 2001; 164(4):669-671.

16. Miyake M, Tateishi U, Maeda T, et al. Pulmonary lymphangioleiomyomatosis in a male patient with tuberous sclerosis complex. Radiat Med 2005; 23(7):525-527.
17. Aubry MC, Myers JL, Ryu JH, et al. Pulmonary lymphangioleiomyomatosis in a man. Am J Respir Crit Care Med 2000; 162(2 Pt 1):749-752.
18. Hancock E, Tomkins S, Sampson J, et al. Lymphangioleiomyomatosis and tuberous sclerosis. Respir Med 2002; 96(1):7-13.
19. Kim NR, Chung MP, Park CK, et al. Pulmonary lymphangioleiomyomatosis and multiple hepatic angiomyolipomas in a man. Pathol Int 2003; 53(4):231-235.
20. DAWSON J. Pulmonary tuberous sclerosis and its relationship to other forms of the disease. Q J Med 1954; 23(90):113-145.
21. Halley DJJ, Hoff M, Hubbeling A, et al. Wat is Tubereuze Sclerose Complex? 2nd ed. Netherlands: Stichting Tubereuze Sclerose Nederland (STSN), 2004.
22. Zonnenberg BA, Stroink H, Lequin MH, et al. Leidraad voor de medische begeleiding van kinderen met tubereuze sclerose. Velp, the Netherlands: Ziekenhuis Velp, 1999; 1-21.
23. Bowen J, Beasley SW. Rare pulmonary manifestations of tuberous sclerosis in children. Pediatr Pulmonol 1997; 23(2):114-116.
24. Foresti V, Casati O, Zubani R, et al. Chylous pleural effusion in tuberous sclerosis. Respiration 1990; 57(6):398-401.

7

# Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature

*European Journal of Neurology, 2009; 16(6):691-696*

Miraude EAPM Adriaensen, M.D., MSc.
Cornelia M Schaefer-Prokop, M.D., Ph.D.
Theo Stijnen, Ph.D.
Debbie AC Duyndam, M.D.
Bernard A Zonnenberg, M.D., Ph.D.
Mathias Prokop, M.D., Ph.D.

## Abstract

**Objective**: To investigate the prevalence of subependymal giant cell tumors (SGCT) in patients with tuberous sclerosis complex (TSC).
**Methods**: We performed a retrospective cross-sectional study in a cohort of 285 patients with known TSC. Institutional review board approval was obtained. We included all 214 TSC-patients who had received a contrast-enhanced computed tomography (CT) scan of the brain. The most recent scan was evaluated for SGCT and presence of hydrocephalus. Additionally, a literature search was performed, and pooled estimates of SGCT prevalence in TSC were calculated. We used descriptive statistics, two sample t-test, chi-squared-test, and meta-analysis as appropriate.
**Results**: Computed tomography showed radiological evidence of SGCT in 43 of the 214 TSC-patients (20%); 23 of 105 men (22%) and 20 of 109 women (18%; P = .52). Average maximum tumor size was 11.4 mm (range, 4–29 mm). Patients with SGCT (mean, 31 years; range, 16–58 years) were on average younger than patients without SGCT (mean, 37 years; range, 10–72 years; P = .007). No association between tumor size and patient age was detected. Nine patients had bilateral SGCT. Hydrocephalus was present in six of the 43 patients (14%). Meta-analysis of reported prevalence and our current study showed that studies using radiological evidence to diagnose SGCT gave a higher pooled estimate of the prevalence of SGCT in TSC (0.16; 95% CI: 0.12, 0.21) than studies using mainly histopathological evidence of SGCT (0.09; 95% CI: 0.07, 0.12).
**Conclusions**: In our cohort, CT demonstrated evidence of SGCT in 20% of TSC-patients. Prevalence of SGCT in TSC is higher in studies using radiological evidence to diagnose SGCT than in studies using histopathological evidence.

## Introduction

Tuberous sclerosis complex (TSC) is an inheritable multiorgan disease. It is an autosomal-dominant neuro-cutaneous disorder characterized by tumors involving many organ systems including brain, heart, kidneys and skin (1). The disease has a birth incidence of approximately one in 5,000 to 10,000 live births (2). The diagnosis of TSC is made clinically. However, the expression and the severity of the disease show substantial variation within as well as between families (3). Therefore, a clinical scoring system was developed that divides the diagnostic criteria for TSC into major features and minor features (4). A subependymal giant cell tumor (SGCT) is one of the major features (4).

Subependymal giant cell tumors are benign, slow-growing tumors of mixed glioneuronal cells including giant cells. SGCT's are typically located near the foramen of Monroe (1). Because of their location and growth potential SGCT's can cause increased intracranial pressure, obstructive hydrocephalus, focal neurologic deficits, and death (1).

In the literature, the reported prevalence of SGCT in TSC varies from 6% to 19% (5–14). Number of included patients with TSC ranged from only 15 patients to 345 patients in a large historical cohort (11;14). The method used to diagnose SGCT in patients with TSC varied substantially between studies.

Our institution is a large national referral center for patients with TSC. Patients are screened and monitored for various manifestations of the disease. The purpose of this study was to re-investigate the prevalence of subependymal giant cell tumors (SGCT) in patients with tuberous sclerosis complex (TSC).

## Methods

### Study design

Our institution is a nationwide tertiary referral center for TSC since 1995. Individuals with TSC are identified through symptoms, through case finding, and through family screening. In March 2007, our institution followed 285 individuals. In this cross-sectional study, we retrospectively reviewed the most recent contrast-enhanced CT

scan of brain for radiological signs of SGCT i.e. a markedly enhancing lesion near the foramen of Monroe (15). Our institutional review board approved this retrospective study and patient informed consent was waived. Patients were included if they had definite TSC (4) and if they had a contrast-enhanced CT scan of the brain available for review. Contrast-enhanced CT scans of the brain were available for review for 214 of the 285 patients with definite TSC (75%). Of the 214 patients, 105 patients were male (49%). Mean age of included patients at the scan date was 36 years. Age ranged from 10 to 72 years.

Computed tomography scans dated from August 1996 to February 2007. Two researchers independently reviewed the CT scans for radiological signs of SGCT and the presence of hydrocephalus. Cases with discrepant ratings were reevaluated in a consensus session. The CT scans were reviewed for the presence of markedly enhancing lesions near the foramen of Monroe. In case of such a lesion, its maximum diameter in the axial plane was measured, and its location (i.e. right-sided or left-sided) was recorded. Presence of hydrocephalus was defined as radiological enlargement of the ventricular system typical for hydrocephalus or the presence of a ventriculoperitoneal drain.

In addition, a Pubmed search of the English language literature was performed in April 2008 to identify papers that reported SGCT in a cohort of patients with TSC. The keywords used were ‘tuberous sclerosis’ and ‘subependymal’. Bibliographies of identified articles were checked to obtain additional references. Two researchers independently extracted data on the studied cohort of patients with TSC, on the number of patients with SGCT, and on the method used to diagnose SGCT by using standardized forms.

**Imaging technique**

Between 1996 and 2007, patients underwent contrast-enhanced CT scan of the brain on a single detector row scanner (AVE, Philips, Best, The Netherlands), or a 16-detector row scanner (Brilliance 16P or MX800 IDT, Philips, Cleveland, OH). A contrast-enhanced scan of the brain was performed after injection of 120 ml of contrast material (iopromide, Ultravist 300, Bayer-Schering, Germany) at 3ml/s.

### Data analysis

Analyses were performed with Excel for Windows (Microsoft Corporation; Redmond, WA, USA) and SAS (Proc nlmixed; SAS, Cary, NC, USA). Descriptive statistics were used. We used two sample t-test to compare means and chi-squared-test to compare proportions as appropriate. Two-sided P-values of 0.05 or less were considered to indicate a significant difference.

In addition, we calculated pooled estimates and 95% confidence interval of the prevalence of SGCT in patients with TSC found in our study, and the reported prevalence of SGCT in patients with TSC found in the English language literature by using the binomial distribution of meta-analysis by Hamza *et al* (16). Pooled estimates were calculated for all included studies, for studies using radiological evidence to diagnose SGCT, and for studies using mainly histopathological evidence to diagnose SGCT.

## Results

Computed tomography demonstrated radiological signs of SGCT in 43 out of 214 patients (20%) (Fig. 1). Radiological evidence of SGCT was seen in 23 out of 105 male patients (22%) and in 20 out of 109 female patients (18%) (P = 0.52). Patients with radiological evidence of SGCT were on average younger than patients without radiological evidence of SGCT. Patients with SGCT had a mean age of 31 years (range, 16 to 58 years) as opposed to patients without SGCT who had a mean age of 37 years (range, 10 to 72 years) (P = 0.007). Maximum diameter in the axial plane of the enhancing lesions near the foramen of Monroe was on average 11.4 mm. Size ranged from 4 mm to 29 mm. Twenty-two SGCT measured at least 1 cm. A scatter plot showed no association between age of the patient and size of the SGCT. Bilateral SGCT were seen in nine out of 43 patients with SGCT (21%) (Fig. 1b). Bilateral SGCT was seen more often in male patients than in female patients. However, this was not significant. Seven out of 23 male patients (30%) had bilateral SGCT, and two out of 20 female patients (10%) had bilateral SGCT (P = 0.10). In total, SGCT were located 19 times on the right and 33 times on the left. Hydrocephalus was only seen in patients with SGCT and not in patients without SGCT. A hydrocephalus was present in six out of 43 patients with SGCT (14%), one of which had been successfully

treated by a ventriculoperitoneal shunt. Mean age of patients who had developed a hydrocephalus was 32 years (range, 21 to 43 years).

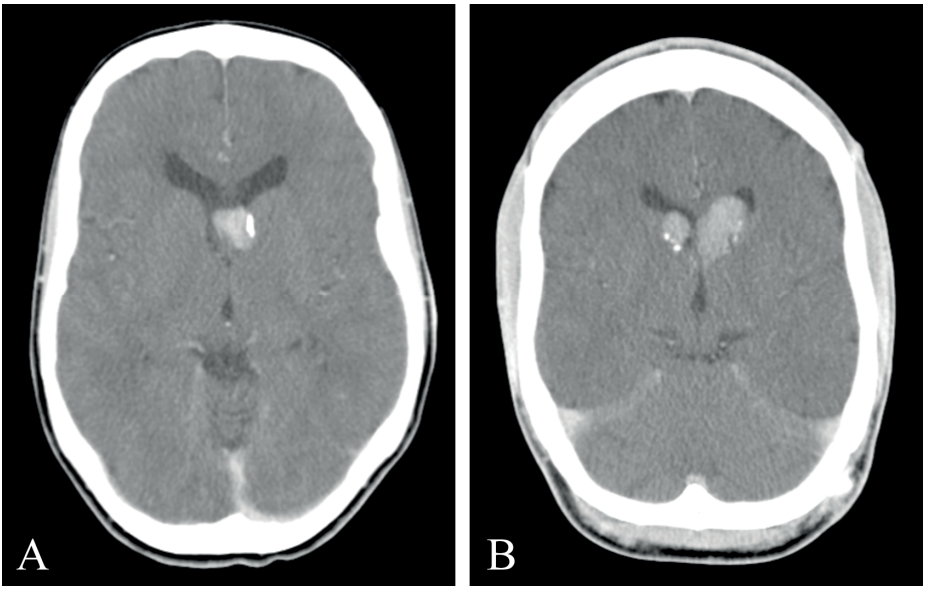



**Figure 1.** Radiological signs of subependymal giant cell tumors in patients with tuberous sclerosis complex on contrast enhanced CT scan of the brain. (a) Unilateral, left-sided enhancing lesion (arrow) near the foramen of Monroe in a 29-year-old, female patient with tuberous sclerosis complex. (b) Bilateral enhancing lesions (arrows) near the foramen of Monroe in a 24-year-old male patient with tuberous sclerosis complex.

Eleven papers were identified in the English language literature that reported SGCT in a cohort of patients with TSC (Table 1) (5–14;17). The reported prevalence of SGCT in TSC varied from 0.06 to 0.19 (Table 1). Twelve studies were included in our meta-analysis i.e. the eleven papers that were identified in the English language literature and our own cohort study. The resulting pooled estimate of the prevalence of SGCT in patients with TSC was 0.11 (95% CI: 0.09, 0.14).

Five studies included in our meta-analysis used radiological evidence to diagnose SGCT (Table 1a). The following definitions to diagnose SGCT were used: a markedly enhancing lesion near the foramen of Monroe on contrast enhanced CT (15), a markedly enhancing lesion after contrast on CT and/or MRI around the foramen of Monroe (10;12), large partly calcified masses around the foramen of Monroe which

frequently enhanced markedly (13), and an intraventricular tumor with slightly higher density than brain on CT and enhancement after contrast (17). The pooled estimate of the prevalence of SGCT in patients with TSC found in the five studies using radiological evidence for diagnosis of SGCT was 0.16 (95% CI: 0.12, 0.21).

Seven studies included in our meta-analysis used mainly histopathological evidence to diagnose SGCT (Table 1b). Four studies reported histopathological evidence of SGCT in all 35 patients identified with SGCT in these studies (5;6;8;14). Histopathological data was obtained from surgical resection or autopsy. Reasons for surgical resection were hydrocephalus, symptoms of increased intracranial pressure, focal neurologic deficit attributable to SGCT, and radiological changes on routine screening imaging (like interval increase in size of SGCT) whilst the patient was still asymptomatic. Two studies reported histopathological evidence of SGCT in the majority of patients identified with SGCT i.e. 25 of 29 patients identified with SGCT (7;11). Nabbout *et al* defined SGCT as any mass measuring > 10 mm in diameter with growth of more than 5 mm on serial radiological imaging. One patient had not undergone surgical removal yet because ventricular dilatation remained stable despite growth of SGCT (7). Shepherd *et al* used clinical and radiological evidence in three patients who had died of a brain tumor without available histological material (11). In the population-based study of Webb *et al* nine patients with symptomatic SGCT were identified; five had successful tumor resection and four died during follow-up (9). The pooled estimate of the prevalence of SGCT in patients with TSC found in the seven studies using mainly histopathological evidence to diagnose SGCT was 0.09 (95% CI: 0.07, 0.12). This is a significantly lower prevalence than in the group of patients diagnosed by radiological criteria of SGCT (0.09 versus 0.16).

**Table 1a.** Summary table of studies reporting prevalence of subependymal giant cell tumors in patients with tuberous sclerosis complex using radiological proof to diagnose SGCT

| Reference | Year of Publication | Study Location | Study Period | Number of TSC-patients total (male) | Study Population | Number of SGCT-patients total (male) | SGCT-patients mean age (range) | Prevalence of SGCT in TSC |
|---|---|---|---|---|---|---|---|---|
| Adriaensen et al[a] | 2008 | Netherlands | 1996–2007 | 214 (105) | A&P | 43 (23) | 31y (16y-58y) | 0.20 |
| Menor et al | 1992 | Spain | n.r.[b] | 27 (15) | P | 5 (n.r.) | n.r. (5m-13y) | 0.19 |
| Altman et al | 1988 | Miami, USA | 1980–1987 | 26 (13) | A&P | 3 (n.r.) | n.r. | 0.12 |
| Kingsley et al | 1986 | London[c] &Toronto | 1974-n.r. | 110 (n.r.) | P | 15 (n.r.) | n.r. (3y6m-19y) | 0.14 |
| Lee et al | 1978 | London[d]&New York | n.r. | 62 (n.r.) | A[e]&P | 6 (n.r.) | n.r. | 0.10 |
| Pooled estimate (95% confidence interval): | | | | | | | | 0.16 (0.12,0.21) |

A = adult population; m = months; n.r. = not reported; P = pediatric population; SGCT = subependymal giant cell tumor; TSC = tuberous sclerosis complex; y = years; [a] Presented at the European Congress of Radiology 2008, Vienna, Austria, March 2008; European Radiology, Volume 18, Supplement 1, February 2008, C-759; [b] CT, MRI and neurological features of 27 children with TSC were prospectively compared. Follow-up over 5 years with CT was available in 17 children.; [c] Great Ormond Street Hospital.; [d] St. Bartholomew's Hospital; [e] Reported age categories range from 6 months to more than 12 years.

**Table 1b.** Summary table of studies reporting prevalence of subependymal giant cell tumors in patients with tuberous sclerosis complex using mainly histopathological proof to diagnose SGCT

| Reference | Year of Publication | Study Location | Study Period | Number of TSC-patients total (male) | Study Population | Number of SGCT-patients total (male) | SGCT-patients mean age (range) | Prevalence of SGCT in TSC |
|---|---|---|---|---|---|---|---|---|
| Goh et al | 2004 | Boston, USA | 2001–2003 | 134 (n.r.) | A&P | 11 (6) | 11y (3y-20y) | 0.08 |
| Cuccia et al | 2003 | Argentina | 1988–2000 | 105 (n.r.) | P | 15 (9) | 11y (4y7m-19y) | 0.14 |
| Nabbout et al | 1999 | France | 1987–1996 | 60 (28) | P | 8 (3) | 2y (2m-7y) | 0.13 |
| Torres et al[a] | 1998 | Dallas, USA | 1989–1996 | 72 (n.r.) | P | 8 (3) | 10y (3y-16y) | 0.11 |
| Webb et al | 1996 | South of England | 1968–1990[b] | 131 (64) | A&P | 9 (3) | 24y (13y-39y) | 0.07 |
| Shepherd et al | 1991 | Mayo Clinic, USA | 1950–1989 | 345 (184) | A&P | 21 (11) | 13y (1y-31y) | 0.06 |
| McMurdo et al | 1987 | San Francisco, USA | n.r. | 15 (8) | P | 1 (n.r.) | n.r. | 0.07 |
| Pooled estimate (95% confidence interval): | | | | | | | | 0.09 (0.07,0.12) |

A = adult population; m = months; n.r. = not reported; P = pediatric population; SGCT = subependymal giant cell tumor; TSC = tuberous sclerosis complex; y = years; [a] Study reports on 19 patients with SGCT and TSC. Eight asymptomatic cases were identified in 72 patients less than 18 years who were enrolled in a surveillance program; [b] All 131 TSC-patients were alive on the census date 31st August 1986.

## Discussion

In the English language literature the reported prevalence of SGCT in TSC varies from 6% to 19% (5–14). Purpose of this study was to re-investigate the prevalence of SGCT in patients with TSC, including new data from a large Dutch cohort that is extensively evaluated by radiological imaging.

Our institution is a national referral center for patients with TSC. Diagnosis of TSC is based on the criteria defined by the consensus conference in 1998 (4). In our retrospective cross-sectional cohort study we found radiological evidence of SGCT - defined as a markedly enhancing lesion near the foramen of Monroe on contrast-enhanced CT scan of the brain - .in 43 out of 214 patients (20%). A meta-analysis of the reported prevalence and our current study using the binomial distribution of meta-analysis by Hamza *et al* (16) showed that studies using radiological evidence to diagnose SGCT gave a higher pooled estimate of the prevalence of SGCT in TSC (0.16; 95% CI: 0.12, 0.21) than studies using mainly histopathological evidence to diagnose SGCT (0.09; 95% CI: 0.07, 0.12).

Subependymal giant cell tumors is one of the three major features within the central nervous system in the diagnostic criteria for TSC. Subependymal nodules (SEN) and cortical tubers are the others. The difference between SEN and SGCT is not always clear. Histopathologically, SEN and SGCT are even described as indistinguishable (5;11). Both lesions are of mixed glioneuronal lineage and contain giant cells. Different radiological criteria have been used in an attempt to distinguish SEN from SGCT. For a yet unknown reason, SGCT almost exclusively occur near the foramen of Monroe. Growth of the lesion, development of hydrocephalus in the presence of an obstructive lesion, development of papilledema as a sign of increased intracranial pressure, or focal neurological deficits attributable to the lesion are considered indications for surgical resection.

No consensus about the radiological signs used as evidence for SGCT has been reached yet. Definitions in the literature vary from any enhancing subependymal lesion in the brain of TSC patients (18) to only markedly enhancing lesions that are located near the foramen of Monroe (15). In our own cohort we have adopted the more conservative approach of only including markedly enhancing lesions near the foramen of Monroe on CT.

Natural history of SGCT is still not fully elucidated (19). Therefore, the exact surgical timing is still controversial. According to Torres *et al*, the growth of SEN and SGCT peaks at puberty, and stops by the end of the third decade of life (20). In most studies, the reported mean age of TSC-patients with SGCT was below 18 years (Table 1). Only the population-based study of Webb *et al* in the South of England reported a mean age of 24 years (9). In our study the mean age was 31 years, and the age of TSC-patients with complicating hydrocephalus ranged from 21 to 43 years. Complicating hydrocephalus was present in 6 out of 43 TSC-patients with SGCT (14%). This could still be an underestimation of the complication rate due to SGCT in TSC-patients as the compliance of the subependymal brain tissue might be altered explaining the occurrence of increased intracranial pressure in some TSC-patients with SGCT without radiological signs of hydrocephalus (5).

The prevalence of SGCT in TSC in studies that used histopathological evidence varied from 0.06 to 0.14. The prevalence of SGCT in TSC in studies that used radiological evidence including our cohort study varied from 0.10 to 0.20. It can be assumed that the studies with histopathological evidence selected the more severe cases as these patients underwent biopsy sampling, surgical resection, or autopsy, which could explain the lower prevalence of SGCT in this group. A similar trend was reported in a population-based study in Wessex (18) that appears to be partially based on the same population as the study reported by Webb *et al* (9). O'Callaghan *et al* reported symptomatic SGCT in 20 out of 179 TSC-patients (5.6%). However, cranial MR imaging in 41 asymptomatic TSC-patients from the same population showed radiologic evidence of SGCT much more frequently: SGCT was seen in 17% to 59% of patients depending upon the radiological criterion used (18).

A limitation of our retrospective cross-sectional cohort, inherent to the retrospective nature of the study, is that we did not have a contrast-enhanced CT scan of the brain available for every patient with TSC followed in our hospital. However, compared with the studies reported in the English language literature, our cohort is still the second largest and the largest using radiological evidence.

Subependymal giant cell tumors are potentially lethal and have been shown to be responsible for 25% of the excess mortality due to TSC (21). Therefore, a long-term follow-up in a large population-based cohort of patients with TSC would be necessary to study the natural history of SGCT into adulthood in order to identify the necessity and optimal frequency of cranial imaging in TSC-patients. Currently, the advice ranges from no cranial imaging to screen for SGCT in asymptomatic indi-

viduals with TSC (18) to yearly cranial imaging in TSC-patients with SENs and SGCTs with shortening of the imaging interval in case of progression of the lesion on imaging (22).

Two other imaging criteria used in an attempt to differentiate SEN from SGCT are growth of the lesion on serial imaging, and a diameter size equal or more than 1cm. Inherent to our cross-sectional study design, growth of all detected SGCT on serial imaging could not be confirmed. In our cohort, 22 out of 214 patients (10.3%) already had a markedly enhancing lesion near the foramen of Monroe measuring at least 1cm in maximum axial diameter. Imaging follow-up of our cohort will be performed.

Our meta-analysis was, of course, limited by the originally reported data and the lack of standardization. To reduce the effect of different interpretation of reported data, two researchers independently extracted the data. Lack of standardization was due to changing diagnostic criteria for TSC over time with study periods varying from 1950 to 2007, and due to lack of a clear definition of SGCT. Furthermore, lack of common reporting standards resulted in missing data (Table 1).

In summary the objective of this study was to investigate the prevalence of SGCT in patients with TSC. In our retrospective cross-sectional study in a large cohort of TSC patients, radiological evidence of SGCT was found in 43 of 214 included patients (20%). A meta-analysis of the reported prevalence in the English language literature, and our current study showed that the prevalence of SGCT in TSC is higher in studies using radiological evidence to diagnose SGCT (0.16; 95% CI: 0.12, 0.21) than in studies using mainly histopathological evidence (0.09; 95% CI: 0.07, 0.12). This suggests that the prevalence of subependymal giant cell tumors in patients with tuberous sclerosis complex is higher than clinically expected, which implies that the proportion of patients that are at risk for developing complications due to SGCT is underestimated based on clinical criteria alone.

## References

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. New England Journal of Medicine 2006; 355(13):1345–1356.
2. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Annals of the New York Academy of Sciences 1991; 615:125–127.

3. Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of expression in tuberous sclerosis. Journal of medical genetics 1993; 30(1):41–43.
4. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. Journal of child neurology 1998; 13(12):624–628.
5. Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 2004; 63(8):1457–1461.
6. Cuccia V, Zuccaro G, Sosa F, Monges J, Lubienieky F, Taratuto AL. Subependymal giant cell astrocytoma in children with tuberous sclerosis. Child's nervous system 2003; 19(4):232–243.
7. Nabbout R, Santos M, Rolland Y, Delalande O, Dulac O, Chiron C. Early diagnosis of subependymal giant cell astrocytoma in children with tuberous sclerosis. Journal of neurology, neurosurgery, and psychiatry 1999; 66(3):370–375.
8. Torres OA, Roach ES, Delgado MR et al. Early diagnosis of subependymal giant cell astrocytoma in patients with tuberous sclerosis. Journal of child neurology 1998; 13(4):173–177.
9. Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: a population study. Developmental medicine and child neurology 1996; 38(2):146–155.
10. Menor F, Marti-Bonmati L, Mulas F, Poyatos C, Cortina H. Neuroimaging in tuberous sclerosis: a clinicoradiological evaluation in pediatric patients. Pediatric Radiology 1992; 22(7):485–489.
11. Shepherd CW, Scheithauer BW, Gomez MR, Altermatt HJ, Katzmann JA. Subependymal giant cell astrocytoma: a clinical, pathological, and flow cytometric study. Neurosurgery 1991; 28(6):864–868.
12. Altman NR, Purser RK, Post MJ. Tuberous sclerosis: characteristics at CT and MR imaging. Radiology 1988; 167(2):527–532.
13. Kingsley DP, Kendall BE, Fitz CR. Tuberous sclerosis: a clinicoradiological evaluation of 110 cases with particular reference to atypical presentation. Neuroradiology 1986; 28(1):38–46.
14. McMurdo SK, Jr., Moore SG, Brant-Zawadzki M et al. MR imaging of intracranial tuberous sclerosis. AJR. American journal of roentgenology 1987; 148(4):791–796.
15. Koeller KK, Sandberg GD. From the archives of the AFIP. Cerebral intraventricular neoplasms: radiologic-pathologic correlation. Radiographics 2002; 22(6):1473–1505.
16. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. Journal of clinical epidemiology 2008; 61(1):41–51.
17. Lee BC, Gawler J. Tuberous sclerosis. Comparison of computed tomography and conventional neuroradiology. Radiology 1978; 127(2):403–407.
18. O'Callaghan FJ, Martyn CN, Renowden S, Noakes M, Presdee D, Osborne JP. Sub-ependymal nodules, giant cell astrocytomas and the tuberous sclerosis complex: a population based study. Archives of disease in childhood 2008;93:751–754.
19. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. Journal of child neurology 1999; 14(6):401–407.
20. Torres VE, King BF, McKusick MA, Bjornsson J, Zincke H. Update on tuberous sclerosis complex. Contributions to nephrology 2001;(136):33–49.
21. Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. Mayo Clinic proceedings. Mayo Clinic 1991; 66(8):792–796.
22. Clarke MJ, Foy AB, Wetjen N, Raffel C. Imaging characteristics and growth of subependymal giant cell astrocytomas. Neurosurgical Focus 2006; 20(1):E5.

# Summary / Samenvatting

**Tuberous sclerosis complex**

Tuberous sclerosis complex (TSC) is an inheritable multiorgan disease. It is an autosomal-dominant neuro-cutaneous disorder characterized by tumor-like malformations involving many organ systems including brain, lungs, heart, kidneys and skin. The classical diagnostic triad of seizures, mental retardation, and facial angiofibromas occurs in less than half of the patients as expression and severity of the disease show substantial variation within as well as between families. Therefore, a clinical scoring system was developed. The current clinical diagnostic criteria for TSC are divided into major features and minor features. No single diagnostic feature is considered pathognomonic for TSC anymore. The diagnosis of definite TSC requires the presence of two major features, or of one major and two minor features. Major features are facial angiofibromas or forehead plaques, shagreen patch, three or more hypomelanotic macules, nontraumatic (peri)ungual fibromas, lymphangioleiomyomatosis, renal angiomyolipoma, cardiac rhabdomyoma, multiple retinal nodular hamartomas, cortical tuber, subependymal nodules, and subependymal giant cell astrocytomas. The list of minor features includes less specific findings and less substantiated signs.

**Imaging in tuberous sclerosis complex**

Since 1995, the University Medical Center Utrecht is a nationwide referral center for patients with TSC. According to national and international guidelines patients with TSC undergo regular imaging at our radiology department.

Aim of this thesis was to initiate a systematic evaluation of imaging in patients with TSC followed at our institution. This thesis focused on imaging of the heart, the lungs and the brain.

*Heart*

There is a discrepancy between the Dutch national TSC guidelines and the international recommendations for diagnostic evaluation in TSC. While the first recommend at least one echocardiogram in all patients to screen for cardiac rhabdomyomas irrespective of the presence of cardiac clinical symptoms, the international consensus guidelines recommend echocardiography only for a selected group of patients dependent on the presence of cardiac symptoms or the need to confirm cardiac lesions for diagnostic purposes. Therefore, in a retrospective study we as-

sessed the frequency of abnormal echocardiographic findings in a cohort of 56 patients with known TSC referred to our cardiology department for screening echocardiography (Chapter 2). Abnormal findings were seen in about one third of patients. The most common abnormal findings were focal areas of increased intramyocardial echogenicity seen in 16 out of 56 patients (29%). Clinical consequence of this finding is still unknown.

During routine evaluation of abdominal CT studies obtained for evaluation of renal angiomyolipomas, we noted abnormal fatty foci in the caudal portions of the heart of these patients. In a case-control study, we examined the morphologic characteristics at CT of such focal fatty foci in the myocardium of patients known to have TSC (Chapter 3). Despite incomplete depiction of the heart with CT and the absence of electrocardiographic gating, the majority of patients with TSC (35 (64%) of 55 patients) demonstrated well-circumscribed foci of fat attenuation in the myocardium that were not present in age- and sex-matched control subjects. In comparison to the known causes of fat in the myocardium (ie epicardial fat deposits, old myocardial infarctions, arrhythmogenic right ventricular dysplasia, normal right ventricular fat, hemangiomas, and liposarcomas), the fatty foci in patients with TSC appear to have unique CT characteristics consisting of a combination of focality, well-circumscribed form, location into the mid myocardium, pure fat density, absence of enhancement, and absence of invasive behavior. On MR these fatty foci show the signal intensity of fat (Chapter 4). On echocardiography fatty foci can be seen as areas of increased echogenicity (Chapter 2).

Subsequently, we investigated in a retrospective study if areas of abnormal myocardium in patients with TSC could also be found in post mortem specimen (Chapter 5). Indeed, two specimens (50%) out of four included specimens of the heart did show areas of mature fat cells in the myocardium, without associated inflammation, without associated fibrosis, without entrapped myocardial cells, and without a capsule which seem to be unique for TSC.

Adding these fatty foci in the myocardium seen on echocardiography, CT, MR and histopathology to the list of major features of TSC may be considered in the future.

*Lungs*

Lymphangioleiomyomatosis (LAM) is characterized by diffusely distributed pulmonary thin-walled cysts with intervening normal lung parenchyma. According to the

literature almost all patients are female. In daily practice we noted male patients with thin-walled cysts in the basal portions of the lungs depicted at abdominal CT scans. Therefore, in a cross-sectional study we reviewed the most recent CT scan of the lung bases for radiologic evidence of LAM in a cohort of 186 included adult patients with known TSC (Chapter 6). Our study demonstrated pulmonary thin-walled cysts with intervening normal lung parenchyma in the lung bases in 28% of adult TSC-patients (52 out of 186 patients). Gender specific prevalence was 0.42 in female (40 out of 95 women) and 0.13 in male TSC-patients (12 out of 91 men).

*Brain*

In the literature the reported prevalence of subependymal giant cell tumors (SGCT) in TSC varied from 0.06 to 0.19. In a cross-sectional study we reviewed the most recent contrast-enhanced CT scan of the brain for radiologic signs of SGCT i.e. a markedly enhancing lesion near the foramen of Monroe in a cohort of 214 included patients with known TSC (Chapter 7). Our study demonstrated radiologic evidence of SGCT in 20% of TSC-patients (43 out of 214 patients). Gender specific prevalence was 0.18 in female (20 out of 109 women) and 0.22 in male TSC-patients (23 out of 105 men).

In addition, a meta-analysis of the reported prevalence in the English language literature, and our own study was performed (Chapter 7). The resulting pooled estimate of the prevalence of SGCT in patients with TSC was 0.11 (95% CI:0.09, 0.14). The prevalence of SGCT in TSC was higher in studies using radiologic evidence to diagnose SGCT (0.16; 95% CI: 0.12, 0.21) than in studies using mainly histopathologic evidence (0.09; 95% CI:0.07, 0.12).

**Tubereuze sclerose complex**

Tubereuze sclerose complex (TSC) is een erfelijke multiorgaanaandoening. Het is een autosomaal dominant erfelijke, neurocutane aandoening gekenmerkt door tumorachtige malformaties in veel organen waaronder de hersenen, de longen, het hart, de nieren en de huid. De klassieke diagnostische triade van epilepsie, mentale retardatie en faciale angiofibromen treedt op in minder dan de helft van het aantal patiënten, omdat de expressie en ernst van de aandoening erg varieert zowel binnen als tussen families. Daarom zijn er klinische diagnostische criteria voor de diagnose TSC ontwikkeld. De huidige diagnostische criteria voor TSC worden onderverdeeld in majeure en mineure criteria. Geen enkel diagnostisch criterium wordt als pathognomonisch beschouwd voor TSC. De diagnose "definitief TSC" vereist de aanwezigheid van 2 majeure criteria danwel 1 majeur criterium en twee mineure criteria. Majeure criteria zijn faciale angiofibromen of voorhoofdplaque, peau de chagrin (bindweefselnaevus), drie of meer hypomelanotische maculae, niet traumatische (sub)unguaal of periunguaal fibroom, lymfangioleiomyomatosis van de longen, angiomyolipomen van de nieren, cardiaal rabdomyoom, multipele retinale nodulaire hamartomen, corticale tubers in de hersenen en subependymale reuscelastrocytomen. De lijst met mineure criteria bestaat uit minder specifieke bevindingen.

**Beeldvorming bij tubereuze sclerose complex**

Sinds 1995 is het Universitair Medisch Centrum Utrecht een nationaal verwijscentrum voor patiënten met TSC. Volgens nationale en internationale richtlijnen ondergaan patiënten met TSC regelmatig beeldvorming op onze afdeling radiologie.

Doel van dit proefschrift was om een begin te maken met de systematische evaluatie van de beeldvorming van patiënten met TSC die gevolgd worden in ons centrum. Dit proefschrift focust op de beeldvorming van het hart, de longen en de hersenen.

*Hart*
Er bestaat een discrepantie tussen de Nederlandse nationale TSC richtlijnen en de internationale aanbevelingen voor de diagnostische evaluatie bij TSC: terwijl de eerste op zijn minst 1 echocardiogram aanbeveelt om te screenen voor rabdomyomen onafhankelijk van de aanwezigheid van cardiale klachten, beveelt de internationale consensus-richtlijn alleen echocardiografie aan voor een selecte groep patiën-

ten indien er sprake is van cardiale symptomen danwel de behoefte bestaat om cardiale lesies te bevestigen voor diagnostische doeleinden. Daarom hebben we in een retrospective studie de frequentie van abnormale echocardiografische bevindingen onderzocht in een cohort van 56 patiënten met TSC die verwezen waren naar onze cardiologie-afdeling voor een screeningsechocardiogram (Hoofdstuk 2). Ongeveer een derde van de patiënten had abnormale bevindingen op het screeningsechocardiogram. De meest voorkomende abnormale bevinding waren focale gebieden met een verhoogde echogeniciteit gelegen in het myocardium die gezien werden in 16 van de 56 patiënten (29%). De klinische consequentie van deze bevinding is nog onbekend.

Tijdens de routinebeoordeling van abdominale CT-onderzoeken vervaardigd ter evaluatie van renale angiomyolipomen, zagen we abnormale vettige foci in het afgebeelde caudale deel van het hart van deze patiënten. In een patiënt-controle-onderzoek bestudeerden we de morfologische kenmerken op CT van deze focale vettige foci in het myocardium van patiënten met TSC (Hoofdstuk 3). Ondanks de incomplete afbeelding van het hart met CT en de afwezigheid van electrocardiografische sturing, had de meerderheid van de patiënten met TSC (35 (64%) van 55 patienten) wel omschreven foci met vetattenuatie in het myocardium die niet aanwezig waren in een voor leeftijd en geslacht overeenkomende controlegroep. In vergelijking met de bekende oorzaken van vet in het myocardium (i.e. epicardiale vetdeposities, oud hartinfarct, aritmogene rechter-ventrikeldysplasie, hemangiomen en liposarcomen) lijken de vettige foci bij patiënten met TSC unieke CT-kenmerken te hebben die bestaan uit een combinatie van focaliteit, welomschrevenheid, lokatie tot in het midmyocardium, pure vetdensiteit, afwezigheid van aankleuring en afwezigheid van invasief gedrag. Op MR tonen deze vettige foci de signaalintensiteit van vet (Hoofdstuk 4). Op echocardiografie worden vettige foci weergegeven als gebieden met een verhoogde echogeniciteit (Hoofdstuk 2).

Aansluitend hebben we in een retrospectieve studie onderzocht of gebieden met afwijkend myocardium ook aanwezig waren in post-mortemspecimen van patiënten met TSC (Hoofdstuk 5). Inderdaad toonden twee speciment (50%) van de vier geïncludeerde specimen gebieden met mature vetcellen, zonder geassocieerde inflammatie, zonder geassocieerde fibrose, zonder ingesloten myocyten en zonder een kapsel die uniek lijken te zijn voor TSC.

Het toevoegen aan de lijst van majeure criteria voor TSC van deze vettige foci in het myocardium die te zien zijn op echocardiografie, CT, MR en histopathologie zou overwogen moeten worden.

*Longen*
Lymfangioleiomyomatosis (LAM) van de longen wordt gekenmerkt door diffuus verspreide, dunwandige, pulmonale cysten met normaal tussenliggend longparenchym. Volgens de literatuur zijn bijna al deze patiënten van het vrouwelijke geslacht. In de dagelijkse praktijk zagen we mannelijke patiënten met dunwandige cysten in het afgebeelde basale deel van de longen op abdominale CT scans. Daarom hebben we in een dwarsdoorsnede-onderzoek de meest recente CT-scan van de basale longvelden beoordeeld op de aanwezigheid van radiologisch bewijs voor LAM in een cohort van 186 geïncludeerde volwassen patiënten met TSC (Hoofdstuk 6). Onze studie toonde pulmonale cysten met normaal tussenliggend longparenchym in de basale longvelden bij 28% van de volwassen TSC-patiënten (52 van de 186 patiënten). Gender-specifieke prevalentie was 0.42 bij vrouwelijke (40 van de 95 vrouwen) en 0.13 bij mannelijke TSC-patiënten (12 van de 91 mannen).

*Hersenen*
De in de literatuur gerapporteerde prevalentie van subependymale reusceltumoren (SGCT) in TSC varieert van 0.06 tot 0.19. In een dwarsdoorsnede-onderzoek beoordeelden we de meest recente CT-scan van de hersenen gescand na toediening van intraveus contrast op de aanwezigheid van radiologisch bewijs voor SGCT (i.e. een fors aankleurende lesie naast het foramen van Monroe) in een cohort van 214 geïncludeerde patiënten met TSC (Hoofdstuk 7). Onze studie toonde radiologisch bewijs voor SGCT bij 20% van de TSC-patiënten (43 van de 214 patiënten). Gender-specifieke prevalentie 0.18 bij vrouwelijke (20 van de 109 vrouwen) en 0.22 bij de mannelijke TSC-patiënten (23 van de 105 mannen).

Aanvullend hebben we een meta-analyse verricht met de in de Engelstalige literatuur gerapporteerde prevalenties en onze eigen studieresultaten (Hoofdstuk 7). De resulterende gepoolde schatting van de prevalentie van SGCT in patiënten met TSC was 0.11 (95% BI:0.09, 0.14). De prevalentie van SGCT in TSC was hoger in studies die radiologisch bewijs gebruikten voor het vaststellen van de diagnose SGCT (0.16; 95% CI: 0.12, 0.21) dan in studies die voornamelijk histopathologisch bewijs gebruikten (0.09; 95% CI:0.07, 0.12).

# Future research

The birth incidence of TSC is approximately one in 5,000 to 10,000 live births (1). However, the true birth incidence is still not known due to the possibility of undiagnosed individuals who are only mildly affected or asymptomatic (2;3). Besides the true birth incidence of TSC, also the natural history, life expectancy, and causes of death in TSC are still not fully elucidated (4). A long-term follow-up in a large population-based cohort of patients with TSC with extensive data collection would be ideal to study the natural history of TSC.

In this thesis, a start was made with the systematic evaluation of imaging in patients with TSC followed at our institution. We performed cross-sectional studies to report the prevalence of radiologic evidence of LAM and SGCT in patients with TSC. Inherent to our cross-sectional study designs, complication rate of recurrent pneumothoraces, recurrent chylothoraces or respiratory failure with the need for transplantation in TSC-patients with radiologic evidence of LAM, and complication rate of growth of SGCT leading to increased intracranial pressure, obstructive hydrocephalus, focal neurological deficits or death in TSC-patients with radiologic evidence of SGCT could not be assessed. Serial imaging and clinical follow-up are necessary to answer these questions.

Optimal frequency of radiologic imaging in patients with TSC is still under discussion. Correlating genotype, phenotype, severity of disease, and imaging findings might identify specific subgroups and lead to optimized radiologic imaging follow-up protocols.

On echocardiography, CT, MR, and histopathology we described fatty foci in the myocardium of patients with TSC which seem to be unique for TSC. Because of its potential diagnostic value awareness amongst cardiologists, pathologists and radiologists should be raised to look for other features of TSC should they encounter these fatty foci in daily practice. The prognostic value of these fatty foci is still unknown.

## References

1. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991; 615:125-127.
2. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet 1998; 351(9114):1490.
3. Schwartz RA, Fernandez G, Kotulska K, Jozwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. J Am Acad Dermatol 2007; 57(2):189-202.
4. Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc 1991; 66(8):792-796.

# Dankwoord

Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift. Een aantal personen wil ik hier in het bijzonder noemen.

Allereerst mijn promotor, prof. dr. M. Prokop, en mijn eerste co-promotor, dr. C.M. Schaefer-Prokop. Geachte professor Prokop, dank u wel dat ik bij u mocht promoveren. Uw kennis en kunde zijn een bron van inspiratie. Beste Cornelia, zonder jouw hulp was dit proefschrift er nooit gekomen. Ik hoop ook in de toekomst nog vaak met jullie samen te kunnen werken en veel van jullie te mogen leren.

Mijn tweede co-promotor, dr. B.A. Zonnenberg. Beste Bernard, zonder patiënten met tubereuze sclerose complex, geen onderzoek naar de beeldvorming bij patiënten met tubereuze sclerose complex. Bedankt voor het coördineren van de tubereuze-sclerose-poli in het UMCU en voor alle levenswijsheden die je mij hebt proberen mee te geven.

Mijn 'derde co-promotor', dr. H.H.H. Feringa. Beste Harm, wat een geluk dat we elkaar in Boston hebben ontmoet. Fijn dat je mijn paranimf wilt zijn.

Drs. D.A.C. Duyndam. Beste Debbie, dank je wel dat ik jouw onderzoek naar de beeldvorming bij patiënten met het tubereuze sclerose complex mocht overnemen toen je naar het OLVG vertrok. Natuurlijk ook bedankt voor de interesse en alle tijd en energie die je sindsdien nog in 'ons onderzoek' hebt gestopt.

Prof. dr. T. Stijnen. Geachte professor Stijnen, dank u wel dat u ook na zoveel jaren weer bereid was om mij zo efficiënt te helpen.

Natuurlijk wil ik ook alle andere co-auteurs danken voor hun bijdrage: drs. M.E.E. Brouha, drs. S.A.P. Cornelissen, dr. M.J. Cramer, prof. dr. P.A.F.M. Doevendans en dr. M.F.M. Oosterhout.

De leden van de commissie bedank ik voor het beoordelen van mijn proefschrift.

Cees, bedankt voor alle lijsten.

Karel en Sven, bedankt voor de technische ondersteuning.

Karin, Eugene, Jan en Roy, bedankt voor jullie hulp bij alle posters, presentaties, figuren en tabellen.

Prof. dr. A. Hofman. Geachte professor Hofman, dank u wel dat u me hebt uitgenodigd om deel te nemen aan het excellente-studentenprogramma van de Nihes.

Prof. dr. M.G.M. Hunink. Beste Myriam, dank je wel voor de mogelijkheden die je me hebt geboden en voor de begeleiding tijdens mijn debuut in de medische wetenschap. Ik heb enorm geboft met zo'n superstart. Succes was bij jou gegarandeerd. Helaas is het me niet gelukt om de 100%-acceptatie voort te zetten na mijn vertrek uit Rotterdam.

G. S. Gazelle, M.D., M.P.H., Ph.D. Dear Scott, thank you very much for all your hospitality, all the things you taught me, and the letters of recommendation afterwards. Boston was really great!

Prof. dr. H.E.M. Kerkkamp. Geachte professor Kerkkamp, dank u wel voor uw helpende hand bij de afronding van dit proefschrift.

De maatschap radiologie Atrium Medisch Centrum Parkstad. Beste maten, bedankt dat jullie me in jullie midden hebben toegelaten.

Dr. R.J.S. Lamers. Beste Rob, bedankt voor al je aansporingen en aanmoedigingen om dit proefschrift toch vooral af te ronden. En natuurlijk bedankt voor de speciale rol die je hebt vervuld bij mijn overgang van AIOS naar gevestigd radioloog.

Dear friends, thank you for your friendship and your patience.
Beste vrienden, bedankt voor jullie vriendschap en geduld.

Mijn vader en andere overleden familieleden in mijn leven zijn onderdeel geworden van de manier waarop ik naar de wereld kijk. Dank jullie wel.

Mijn oudtante. Lieve tante Diny, bedankt voor al uw liefde en de grote positieve invloed die u op mijn leven heeft gehad.

Lieve mama en lieve Gwijde, ik had me geen fijnere broer en betere moeder kunnen wensen. Bedankt voor jullie liefde en onvoorwaardelijke steun.

Lieve Fons, bedankt dat je in mijn leven bent gekomen. Ik hou van jou.

# Publications

**Adriaensen MEAPM**, van Oosterhout MFM, Feringa HHH, Schaefer-Prokop CM, Zonnenberg BA, Prokop M. Mature fat cells in the myocardium of patients with tuberous sclerosis complex. J Clin Pathol. 2011; Jan 7 [Epub ahead of print] (Chapter 5)

**Adriaensen MEAPM**, Feringa HHH, Schaefer-Prokop CM, Cornelissen SAP, Zonnenberg BA, Prokop M. Focal fatty areas in the myocardium of patients with tuberous sclerosis complex: a unique finding. J Thorac Imaging. 2011; 26(1):W12-W13 (Chapter 4)

Cornelissen SA, Prokop M, Verhagen HJ, **Adriaensen MEAPM**, Moll FL, Bartels LW. Detection of occult endoleaks after endovascular treatment of abdominal aortic aneurysm using MR imaging with a blood pool contrast agent: preliminary observations. Invest Radiol. 2010; 45(9):548–553

**Adriaensen MEAPM,** Cramer MJM, Brouha MEE, Schaefer-Prokop CM, Prokop M, Doevendans PA, Zonnenberg BA, Feringa HHH. Findings in screening echocardiography in patients with tuberous sclerosis complex. Tex Heart Inst J. 2010; 37(3):280–283 (Chapter 2)

**Adriaensen MEAPM**, Mulhall KJ, Borghans RAP, Magill P, Kavanagh EC. Transient osteoporosis of the hip and spontaneous osteonecrosis of the knee: a common etiology? Ir J Med Sci. 2009; Aug 7 [Epub ahead of print]

**Adriaensen MEAPM**, Schaefer-Prokop CM, Duyndam DAC, Zonnenberg BA, Prokop M. Fatty foci in the myocardium: a common finding on CT in patients with tuberous sclerosis complex. Radiology 2009; 253(2):359–363 (Chapter 3)

**Adriaensen MEAPM**, Schaefer-Prokop CM, Stijnen T, Duyndam DAC, Zonnenberg BA, Prokop M. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis complex and a review of the literature. Eur J Neurol. 2009; 16(6):691–696 (Chapter 7)

Schijf LJ, **Adriaensen MEAPM**, De Klerk JMH, Baarslag HJ, Heggelman BGF, Schaefer-Prokop CM. Pleural and peritoneal mesothelioma: imaging findings on CT and FDG PET/CT. Eur J Radiol. Extra 2009; 69(3):e89-e92

**Adriaensen MEAPM**, Schijf LJ, de Haas MJ, Huijbregts JE, Baarslag HJ, Staaks GHA, de Klerk JMH. Six synchronous primary neoplasms detected by FDG-PET/CT. Eur J Nucl Med Mol Imaging 2008; 35(10):1931

Kock MCJM, **Adriaensen MEAPM**, Pattynama PMT, van Sambeek MRHM, van Urk H, Stijnen T, Hunink MGM. Digital subtraction angiography compared with multidetector row CT angiography in patients with peripheral arterial disease: a randomized controlled trial. Radiology 2005; 237(2):727–737

**Adriaensen MEAPM**, Kock MCJM, Stijnen T, Sambeek MRHM van, Urk H van, Pattynama PMT, Hunink MGM. Peripheral arterial disease: therapeutic confidence in CT versus digital subtraction angiography and effects on additional imaging recommendations. Radiology 2004; 233(2):385–391

Bosch JL, Kaufman JA, Beinfeld MT, **Adriaensen MEAPM**, Brewster DC, Gazelle GS. Cost-effectiveness of elective endovascular and open surgical repair for patients with abdominal aortic aneurysms. Radiology 2002; 225(2):337–344

**Adriaensen MEAPM**, Bosch JL, Halpern EF, Hunink MGM, Gazelle GS. Elective endovascular versus open surgical repair of abdominal aortic aneurysms: a systematic review of short-term results. Radiology 2002; 224(3):739–747

## Abstract presentations

**Adriaensen MEAPM**, Borghans RAP, Hogan B, Al Bulushi HIJ, Kavanagh EC. Double bundle ACL anatomy at 3 Tesla. Presented at the 15th Dutch National Radiological Conference, Veldhoven, the Netherlands. September 2010. Syllabus Radiologendagen 2010: 35

Ertl OT, van Laar PJ, van der List MPJ, Nix M, **Adriaensen MEAPM**. Avoid interpretive difficulties and use a posterior approach in MR arthrography of the shoulder. Presented at the 17th Annual Congress of the European Society of Musculoskeletal Radiology, Lille, France. June 2010. Skeletal Radiology 2010

**Adriaensen MEAPM**, Hogan B, Al Bulushi HIJ, Kavanagh EC. Double bundle ACL anatomy at 3 Tesla. Presented at the 16th Annual Congress of the European Society

of Musculoskeletal Radiology, Genua, Italy. June 2009. Skeletal Radiology 2009; 38: 603

**Adriaensen MEAPM**, Schaefer-Prokop CM, Duyndam DAC, Zonnenberg BA, Prokop WM. Fatty foci in the heart of patients with tuberous sclerosis complex: a unique finding on CT. Presented at the European Congress of Radiology, Vienna, Austria. March 2009. European Radiology 2009; ECR 2009 Book of Abstracts: S196

**Adriaensen MEAPM**, Ertl OT, Schijf LJ, Van der List MPJ, Nix M, Van Laar PJ. Are orthopedic surgeons right when requesting a posterior approach in MR arthrography of the shoulder? Presented at the 13th Dutch National Radiological Conference, Rotterdam, the Netherlands. October 2008. Memorad 2008; 3: 58–59

**Adriaensen MEAPM**, Schaefer-Prokop CM, Stijnen T, Duyndam DAC, Zonnenberg BA, Prokop M. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. Presented at the 9th International Research Conference on Tuberous Sclerosis Complex, Brighton, UK. September 2008

**Adriaensen MEAPM**, Ertl OT, Baarslag HJ, Gietema HA, Nix M. A rare cause of carpal tunnel syndrome diagnosed with high resolution ultrasonography. Presented at the 15th Annual European Society of Musculoskeletal Radiology Meeting, Galway, Ireland. June 2008.

**Adriaensen MEAPM**, Duyndam DAC, Zonnenberg BA, Prokop M. Prevalence of subependymal giant cell tumors in a large cohort of patients with tuberous sclerosis complex and preliminary results of a non-invasive treatment. Presented at the European Congress of Radiology, Vienna, Austria. March 2008. European Radiology 2008; ECR 2008 Book of Abstracts: 493

**Adriaensen MEAPM**, Duyndam DAC, Zonnenberg BA, Prokop M. Radiological Evidence of Lymphangioleiomyomatosis in Female and Male patients with Tuberous Sclerosis Complex. Presented at the 92nd Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, USA. November 2006. Scientific Assembly and Annual Meeting Program: 686

**Adriaensen MEAPM**, Duyndam DAC, Cramer MJM, Zonnenberg BA, Oosterhout MFM van, Prokop WM. Fatty foci in the heart of patients with tuberous sclerosis

complex: a newly described finding on CT. Presented at the World Congress of Cardiology 2006, Barcelona, Spain. September 2006. European Heart Journal 2006; 27 (Abstract Supplement): 425

**Adriaensen MEAPM**, Duyndam DAC, Cramer MJM, Zonnenberg BA, Oosterhout MF van, Prokop WM. Fatty foci in the heart of patients with tuberous sclerosis complex: a newly described finding on CT. Presented at the 91st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, USA. November 2005. Scientific Assembly and Annual Meeting Program: 632

**Adriaensen MEAPM**, Kock MCJM, Stijnen T, Sambeek MRHM van, Urk H van, Pattynama PMT, Hunink MGM. Diagnostic and therapeutic impact of CT angiography compared with digital subtraction angiography for peripheral arterial disease. Presented at the 88th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, USA. December 2002. Radiology 2002; Supplement 225: 157

**Adriaensen MEAPM**, Kock MCJM, Stijnen T, Sambeek MRHM van, Urk H van, Pattynama PMT, Hunink MGM. Comparison of diagnostic and therapeutic impact of two diagnostic imaging techniques for peripheral arterial disease. Presented at the 24th Annual Meeting of the Society for Medical Decision Making, Baltimore, USA. October 2002. Med Decis Making 2002; 22(6): 539

**Adriaensen MEAPM**, Kock MCJM, Stijnen T, Sambeek MRHM van, Urk H van, Pattynama PMT, Hunink MGM. Diagnostic and therapeutic impact of CT angiography compared with digital subtraction angiography for peripheral arterial disease. Presented at the 7th Dutch National Radiological Conference, Noordwijkerhout, the Netherlands. September 2002. Memorad 2002; 3: 24

**Adriaensen MEAPM**, Bosch JL, Halpern EF, Hunink MGM, Gazelle GS. Endovaskulaeres Stenting im Vergleich zur offenen Aneurysmaoperation bei abdominellen Aortenaneurysma: Eine Meta-Analyse der Kurzzeitergebnisse. Presented at the 119. Kongress der Deutschen Gesellschaft fuer Chirurgie, Berlin, Germany. May 2002. Chirurgisches Forum 2002 fur experimentelle und klinische Forschung. 31. Berlin, Springer-Verlag, 2002:539–541, ISBN 3–540–43300–7

**Adriaensen MEAPM**, Kock MCJM, Stijnen T, Sambeek MRHM van, Urk H van, Pattynama PMT, Hunink MGM. Comparison of diagnostic and therapeutic impact of CT angiography with digital subtraction angiography for peripheral arterial disease. Presented at the Netherlands Forum for Medical Decision Making, Scientific Meeting 2002, Amsterdam, the Netherlands. April 2002

**Adriaensen MEAPM**, Bosch JL, Halpern EF, Hunink MGM, Gazelle GS. Endovascular repair is superior to open surgical repair in a meta-analysis of short-term results. Presented at the 87th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, USA. November 2001. Radiology 2001; Supplement 221: 321

**Adriaensen MEAPM**, Bosch JL, Halpern EF, Hunink MGM, Gazelle GS. Elective endovascular versus open surgical repair of abdominal aortic aneurysms: a meta-analysis of short-term results. Presented at the 23rd Annual Meeting of the Society for Medical Decision Making, San Diego, USA. October 2001. Med Decis Making 2001; 21: 536

# Curriculum Vitae

Miraude Adriaensen was born on August 21, 1978 in Deurne, the Netherlands. She attended secondary school at the St.-Willibrord Gymnasium in Deurne from 1990 to 1994. In 1995, she obtained her high school diploma (7 A levels) at the Luzac College in Roermond, the Netherlands. The next year she participated in the Charlemagne Programme, under the patronage of the European parliament and the European commission for culture and education, studying languages in London and Brussels and obtained the European Year certificate and the certificate in advanced English (grade A) from the University of Cambridge. In 1996 she started her medical studies at the Vrije Universiteit Brussel, Belgium, and in October 1996 she continued her medical studies at the Erasmus University Rotterdam, the Netherlands. In August 1997, she received her propedeuse (pre-medical examination) cum laude and was awarded the Prijs Hoogeschool Fonds 1920. In 1998, she entered the Master of Science program in Health Services Research at the Netherlands' institute for health sciences (Nihes) for which she followed courses at Erasmus University Rotterdam (NL), University of Utrecht (NL), University of Cambridge (UK), and Harvard School of Public Health (Boston, USA) (grade A+). Alongside her studies she participated in research at the department of Neuroanatomy (1997–1998) and the department of Public Health and Epidemiology & Biostatistics (1998–2000), she taught the course 'study skills for freshmen' (1997–1998), she was one of the student representatives (1998–2000), she attended her first rotation at the department of radiology of Vienna University Hospital and Medical School (AKH, Vienna, Austria) through the IFMSA (International Federation of Medical Students' Association), and she was a member of the organization committee for the annual national medical students congress held in 1999 and 2000. After receiving her master's degree in medicine (cum laude) and her MSc in Health Services Research both in the summer of 2000, Miraude spent a year as research fellow at Massachusetts General Hospital in Boston (USA) and was appointed as a member of the professional staff of MGH and as a Harvard Officer at Harvard University. Among the six grants she received to finance her stay in Boston were a NAF (Netherland-America Foundation) Fellowship, and a Dutch governmental grant, the so-called Award for Talented Students, awarded by the Ministry of Education to the top 5% of Dutch graduates who finished their studies with excellent results and also impressed the selection committee with their extra-curricular activities and their motivation to study abroad. After she returned to Rotterdam and before she could start her hospital rotations, she worked five months as a researcher at the department of Epidemiology & Biostatistics, and the department of Radiology and lectured fourth year medical students about clinical epidemiology in interactive sessions. In parallel

with her hospital rotations (2/2002–12/2003), Miraude spoke at international and national conferences and saw her research published, for which she received a Stichting Hippocrates Studie-fonds prijs 2003, awarded yearly to Dutch medical students for scientific research performed before receiving their medical degree. She also continued to be a student representative at the Erasmus University Rotterdam and was a member of the LOCA (Landelijk Overleg Co-Assistenten; national organization of 'rotationists') (2002–2003). In February 2003, she returned to Boston to attend a one month's clerkship at the department of cardiac surgery, Children's Hospital, Harvard Medical School, Boston, USA. Upon receiving her MD degree (cum laude) at the Erasmus University Rotterdam on the 19th of December 2003, she was awarded the Studieprijs van het Bataafsch Genootschap der Proefondervindelijke Wijsbegeerte in September 2004, as the best medical graduate in Rotterdam of the year 2003. In February 2004, she started her residency in radiology at the University Medical Center Utrecht, the Netherlands. From January 2007 onwards, she was trained at the Meander Medical Center in Amersfoort, the Netherlands. Since August 1, 2008, she is registered as a radiologist. The end of 2004 in parallel with her residency, Miraude started the research project described in this thesis. She was awarded the Introduction to Research for International Young Academics stipend of the Radiological Society of North America in 2007. Furthermore, as a resident she was a member of the daily board of the LVAG (Landelijke Vereniging voor Medisch Specialisten in Opleiding; national organization of residents), she was the Dutch resident delegate to the PWG (Permanent Working Group of European Junior Doctors; for which she travelled to Helsinki (Finland), Cefalú (Italy), Porto (Portugal), Berlin (Germany), Brdo (Slovenia), Bergen (Norway), and Tallinn (Estonia)), she was the European radiology resident to the UEMS (European Union of Medical Specialists) section of Radiology, she was a member of the central board of the LAD (Landelijke vereniging van Artsen in Dienstverband; national association of salaried doctors), and she was elected as a PWG delegate to the CESME (Council for European Specialist Medical Examinations).

In 2008, she was the first Dutch resident in radiology to receive one of the visiting scholarships offered by the European School of Radiology and spent three months at the Mater Misericordiae University Hospital in Dublin, Ireland, to subspecialize in musculoskeletal radiology. In 2010, she received the diploma of the European Society of Musculoskeletal Radiology. Since 2009, she works as a radiologist at Atrium Medical Center Parkstad, Heerlen, the Netherlands.