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Does the tuberous sclerosis complex include intracranial aneurysms?

A case report with a review of the literature

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Abstract *Background.* Tuberous sclerosis is a protean, genetically determined disease that may involve any organ or tissue and lead to a great number of symptoms and clinical features.

Objective. Diagnosis can be very difficult in cases with incomplete manifestations (formes frustes) lacking the classic signs of the disease.

Materials and methods. We report a case fulfilling the diagnostic criteria for tuberous sclerosis (shagreen patches, hypomelanotic macules, renal cysts and angiomyolipomas, and “migration tracts” in the cerebral white matter) in association with a giant intracranial aneurysm, but lacking mental retardation, epilepsy and facial angiofibroma.

Results. Fourteen other cases of tuberous sclerosis and intracranial aneurysms, all but one without any clear sign of polycystic kidney disease, were found in the literature.

Conclusion. We suggest that vascular dysplasias in general and aneurysms (mainly intracranial) in particular can be added to the other non-primary diagnostic features for the clinical diagnosis of tuberous sclerosis.

Introduction

Tuberous sclerosis complex (TSC) is the archetype of disorders intermediate between blastomatous processes and dysplastic states. It belongs to the group of diseases described by the term “phakomatoses” by Van der Hoeve (1933) or “neuroectodermal dysplasias” by van Bogaert (1935) [1].

Because TSC is a disease with protean clinical manifestations, any organ or tissue may be involved, leading to a myriad of symptoms and associations of symptoms. Indeed, the clinical features of TSC vary considerably and the classic diagnostic triad, first described by Vogt (1908), i.e. mental deficiency, epilepsy and facial angiofibromas, may be lacking. Epilepsy, with or without mental retardation, is the most common clinical presentation. Facial angiofibroma (once called “adenoma se-

baceum”) is the most readily recognised feature of tuberous sclerosis, and without this sign the disease may pass unrecognised. Retinal lesions called “phakomata” may also occur. Besides these more common features, a whole range of other signs and symptoms of variable importance, caused by neurological, renal, cardiac, pulmonary, osseous and cutaneous dysplasias, can be present [1, 2].

Diagnosis is easy in patients in whom epilepsy, facial angiofibroma and intellectual deficits predominate, either with or without other minor symptoms. Conversely, diagnosis is very difficult when manifestations are incomplete (‘formes frustes’ cases). In these patients, molecular investigation for the TSC genes may be helpful, particularly when only secondary or tertiary features are present [3]. Cases have been reported in which the subungual lesions, the so-called Koenen tumours, were

Fig.1 Midline, elevated, low-back mass covered by “orange peel” skin

Fig.2 Anteroposterior radiograph of the lumbar spine showing multiple sclerotic pedicles from T12 to L4 (*arrows*)

Fig.3 Sagittal T1-weighted MRI of the brain showing a right parasellar lesion compatible with a giant right ICA aneurysm (*arrow*)

Fig.4 MRA of the intracranial vessels. The right ICA aneurysm is fusiform in shape (*arrows*) and the left ICA is normal (*arrowheads*)

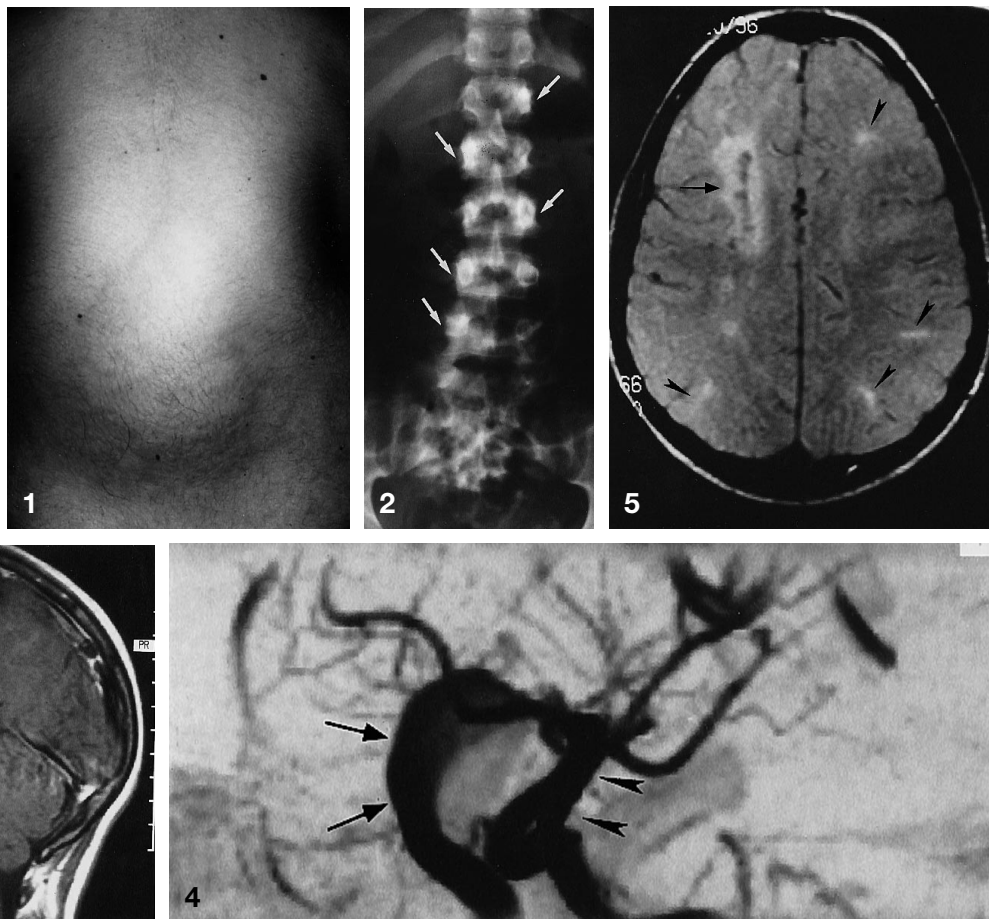


Fig.5 Axial proton density brain MRI showing a hyperintense area in the white matter of the right frontal region (*arrow*) consistent with an ischaemic lesion. There are bilateral linear white-matter hyperintensities radiating from the surface of the brain to the ventricles (*arrowheads*), compatible with “migration tracts”

the sole clinical manifestation of tuberous sclerosis [4]. Other partial forms may show only neurological manifestations, namely epilepsy, mental retardation or subependymal tumours. In addition, a correct diagnosis is particularly difficult in those cases which occur with purely cardiac, renal, hepatic or pulmonary lesions in the absence of any cutaneous and brain lesions [1]. Tsukada and Pickren [5] made the diagnosis incidentally during an autopsy on a woman who died from carcinoma of the breast, and who completely lacked the three major symptoms.

We report on a patient with TSC without mental retardation, epilepsy and facial angiofibroma who showed a giant intracranial aneurysm. The relative frequency of this association is discussed, and a critical review of the literature is presented.

Case report

A normally developed 11-year-old boy was referred for investigation of a low midline back mass suspected as being a pre-sacral lipoma. On examination, a huge depigmented skin area was evident at the antero-lateral surface of the right thigh. Facial angiofibroma, subungual fibroma and retinal hamartomas were absent. Seizures and other neurological abnormalities were absent from his past history. A midline elevated lesion, 10 cm in diameter and covered by pale skin with the texture of orange peel, was evident (Fig.1). Ultrasound showed it to be hypoechoic, containing hyperechoic bundles, and compatible with sub-epidermal fibrosis (“shagreen patch”).

X-rays of the lumbar spine demonstrated sclerosis of the posterior margins of several thoraco-lumbar vertebrae and pedicles from T12 to L4 (Fig.2). To exclude bone metastases from abdominal or intracranial neurogenic tumours, abdominal ultrasound (US) and cranial magnetic resonance imaging (MRI) were performed. US showed a small right kidney containing cysts, the largest being 5 cm in diameter. In the cortex of the left kidney were multiple non-shadowing hyperechoic foci compatible with angiolipomas. On MRI of the brain, a giant right internal carotid artery (ICA) aneurysm, 2 cm in diameter, was evident (Fig.3). The aneurysm, originating from the supra-clinoid portion of the ICA, showed neither thrombosis nor calcification. Magnetic resonance angiography showed the aneurysm to be fusiform in shape. The left ICA was normal (Fig.4). Based on these findings, a diagnosis

of giant ICA aneurysm in the presence of presumptive TSC was made. Ten days later, conventional angiography confirmed the MRI findings. In the same session, endovascular occlusion of the right ICA was undertaken. Mild left hemiparesis developed 3 h later, but cleared completely by 72 h. MRI 2 months later showed an ischaemic lesion in the white matter of the right frontal lobe. Furthermore, bilateral white matter abnormalities radiating from the surface of the brain to the ventricles were evident (Fig. 5). Both parents and the 16-year-old sister of the patient underwent complete clinical examination, including dermatological and ophthalmological evaluations, MRI of the brain and abdominal US. Two hepatic cysts were demonstrated in the patient's father, and a huge depigmented skin area was evident on the trunk of the sister; no abnormalities were detected in the patient's mother. At follow-up 3 years later, the child was perfectly well.

Genetics

All four family members (the patient, his parents and sister) underwent genetic evaluation. For molecular analysis, 8 µg of DNA extracted from peripheral blood leucocytes [6] were double-digested with EcoRI and HindIII restriction enzymes and analysed by Southern blot after 0.8% agarose gel electrophoresis. The TSC2 probe used was a mix of the ³²P-labelled cDNA clones 4B2 and 4.9, a kind gift from J. Sampson [7]. The TSC1 genomic configuration was tested by two overlapping polymerase chain reaction (PCR) fragments (exons 3–16 and 15–23), that spanned the entire TSC1 coding sequence [8]. The genotype at polymorphic markers located within the TSC2 gene, an insertion/deletion of an Alu sequence in intron 2, a minisatellite in intron 8 (N.M. unpublished) and an EcoRV RFLP in exon 40 [9], and in the untranslated 3' tail of PKD1, the microsatellite KG8, were assessed by PCR as previously described [10]. Mutation analysis of the entire TSC2 and of the 2/3 TSC1 (i.e., exons 15–23) was performed with the protein truncation test (PTT). Southern blot analysis of the proband DNA from leucocytes did not show any apparent rearrangement of the expected TSC1 and TSC2 gene configurations. Moreover, at autoradiography, the intensity of each EcoRI and HindIII fragment was not reduced when compared with the band pattern of normal controls, suggesting that both TSC1 and TSC2 alleles were preserved. Four TSC2 and PKD1 intragenic polymorphisms were typed in the patient and in his relatives, but none was informative. However, the contribution of both paternal and maternal 16p13.3-linked alleles was confirmed by testing two and one markers (HBAP1, D16S521 and D16S291) telomeric to TSC2 and centromeric to PKD1, respectively.

The screening by PTT for either nonsense or frameshift mutations in the full-length TSC2 transcript and in approximately two-thirds of the 3' end of TSC1 did not show evidence of truncated proteins.

Discussion

A revision of the TSC diagnostic criteria [11] showed that 45% of individuals affected with TSC have normal intelligence, only 29% present the complete Vogt triad and 6% have none of these three features. On this basis, the classic Vogt triad has been replaced by a modern and more inclusive set of diagnostic criteria [12] (Table 1), so that TSC can be diagnosed by the presence of even only one type of lesion from a list of several unique

Table 1 Diagnostic criteria for tuberous sclerosis complex (TSC) (*hist.* histologic confirmation, *Rx* radiographic evidence). Primary diagnostic criteria are in bold; secondary are in italics; tertiary are in roman

Brain
Subependymal nodule or giant cell astrocytoma (hist.)
Cortical tuber (hist.)
Multiple calcified subependymal nodules protruding into the ventricle (Rx)
<i>Cerebral tubers (Rx)</i>
<i>Noncalcified subependymal nodules (Rx)</i>
Cerebral white-matter "migration tracts" or heterotopias (Rx)
Infantile spasms
Skin
Facial angiofibroma
Multiple unguinal fibromas
<i>Shagreen patch</i>
<i>Forehead plaque</i>
Hypomelanotic macules
"Confetti" skin lesions
Eye
Multiple retinal astrocytomas
<i>Other retinal hamartoma or achromic patch</i>
Heart
<i>Cardiac rhabdomyoma (hist. or Rx)</i>
Kidney
<i>Renal angiomyolipoma (hist. or Rx)</i>
<i>Renal cysts (hist.)</i>
Renal cysts (Rx)
Lung
<i>Pulmonary lymphangiomyomatosis (hist.)</i>
Pulmonary lymphangiomyomatosis (Rx)
Bone
Bone cysts (Rx)
Mouth
Randomly distributed enamel pits in deciduous and/or permanent teeth
Gingival fibromas
Others
<i>Affected first-degree relative</i>
Hamartomatous rectal polyps (hist.)
Hamartoma of other organs (hist.)
Definite TSC
One primary feature, two secondary features of one secondary plus two tertiary features
Probable TSC
Either one secondary plus one tertiary feature or three tertiary features
Suspect TSC
Either one secondary feature or two tertiary features

findings that are usually multiple in TS but are only rarely found in the normal population. By means of these criteria, we may distinguish the patients with a definite diagnosis from those who present subtle or incomplete features of TS [3]. The disease is inherited as an autosomal dominant trait. However, up to 70% of

Table 2 Tuberos sclerosis and intracranial aneurysms: review of the literature (*ACA* anterior cerebral artery, *AML* angio-myolipoma, *ICA* internal carotid artery, *MCA* middle cerebral artery, *ADPKD* autosomal dominant polycystic kidney disease, *SEN* subependymal nodules, *VA* vertebral artery)

Case no./age/sex	Reference	Aneurysm	Associated features
1/12 years/F	[26]	ICAs bilateral, fusiform	Hypomelanotic macules Facial angiofibroma Ungual fibromas Calcified SENs
2/24 years/M	[28]	MCA, saccular	ADPKD Kidney AMLs
3/26 years/F	[35]	intraventricular (necropsy)	Vogt triad Kidney AMLs Hypomelanotic macules Ungual fibromas Liver, spleen and lung hamartomas Cortical tubers SENs
4/17 years/F	[29]	ICA giant + ACA	Facial angiofibroma Hypomelanotic macules Mental handicap Seizures
5/53 years/M	[27]	ICA giant	Hypomelanotic macules Retinal hamartoma
6/7 years/M	[20]	ACA giant, enlarging	Hypomelanotic macules Seizures
7/6 years/F	[30]	ICA giant, fusiform + ACA	Hypomelanotic macules Moderate mental handicap Seizures
8/6 years/F	[31]	ICA giant, fusiform + ACA	Seizures Mental handicap Hypomelanotic macules
9/29 years/M	[33]	ICA giant + VA calcified	Abdominal aneurysm and aorta coarctation Facial angiofibroma Ungual fibroma Hypomelanotic macules Scoliosis Left hemiparesis SENs calcified
10/35 years/F	[2]	ICA giant	Mental handicap Seizures
11/1 year/M	[32]	ACA arteritis	Seizures Mental handicap
12/young boy/M	[22]	VA giant	
13/5 months/M	[34]	ICA giant, fusiform + ACA, MCA ectasias	Seizures Subependymal tumor Retinal hamartoma Hypomelanotic macules
14/30 years/M	[39]	MCA saccular	ADPKD Seizures Mental handicap Facial angiofibroma SENs calcified Cortical tubers

cases are due to a new germ-line mutation. Linkage studies have established genetic heterogeneity, with two TSC genes mapped to chromosome 9 (TSC1) and to chromosome 16 (TSC2), respectively [13, 14]. Hamartomas require complete loss of function of the two alleles at either TSC locus; the first mutation is inherited,

whereas the second allele is mutated somatically. The number and tissue distribution of the second somatic mutations may in part account for the protean manifestations of TSC. Indeed, even within the same family a given mutation may be associated with a variety of clinical phenotypes, including “formes fruste”, which may

be confusing both to the clinician and to the radiologist [15].

With regard to bone lesions, several isolated case reports have described abnormalities of the lumbosacral spine and pelvis in TSC [16–18] with a prevalence as high as 40% [19]. In the list of diagnostic criteria for TSC (Table 1), cysts are the only bone lesion mentioned. However, the most commonly reported osseous involvement is sclerotic (or osteoblastic) lesions affecting the edges of vertebral bodies and pedicles of any portion of the lumbosacral spine and pelvis. The roentgenographic appearance is characteristic, being virtually diagnostic of the disease. When the lesion is less pronounced, it may simulate purely osteoblastic metastases [19]. Bony changes have not been emphasised in the literature and tend to be overlooked, probably because they are asymptomatic. Thus, bone lesions are considered of little diagnostic significance [11].

Although dysplasias and hamartomatous proliferations of small blood vessels, including haemangiomas, are common in TSC, involvement of the medium-sized and large vessels, including aneurysms, is considered rare.

Arterial lesions have previously been described in TSC. Histologically, elastic fibres of the affected arteries are deficient and fragmented, and there is accumulation of mucopolysaccharides in arterial walls. Vascular occlusions, ectasias and/or microaneurysms may result from these changes. Dysplasias of the cerebral vasculature can also occur in NF1 [20]; most commonly, these dysplastic abnormalities consist of intimal proliferation, with resultant stenosis or occlusion of the carotid or proximal middle cerebral artery (MCA) or anterior cerebral artery (ACA), resulting in the moyamoya phenomenon in 60–70% of these patients. Less commonly, cerebral aneurysms may also be detected [21].

Johnson and Gomez [22] reported one case of coarctation of the aorta in a 9-day-old infant with TSC proven at post-mortem examination. Nine TSC patients with an aortic aneurysm [23] and one with an axillary artery aneurysm [24] have been reported in the literature. Moreover, the association of TSC with fibromuscular dysplasia of the aneurysmal vessel has been described [24, 25].

In our review of the literature, we found 14 patients with intracranial aneurysms, originating mostly from the ICA [2, 26–34], ACA [20, 28–31, 33] or MCA [33–35]. Occasionally, the aneurysm was intraventricular in location [36] or originated from the vertebral artery (VA) [22, 33]. In 6/14 patients, the aneurysms were multiple [26, 28–30, 32, 33] (Table 2). It is of some interest that 9/15 patients with TSC and intracranial aneurysms (including the present case report) presented with ICA aneurysm (isolated or associated). This percentage (60%) is much higher than the overall incidence of ICA aneurysms (31%) [37], whereas the

percentage of ACA aneurysms is in line with the reported usual distribution (43% vs 41%). There is no clear explanation for this result. Only three of these patients were older than 30 years of age at the time of diagnosis (Table 2, cases 5, 10 and 14), and in 9 patients the aneurysm was giant (cases 4–10, 12 and 13).

The pathogenesis of intracranial aneurysms is unclear. Certainly, the young age of these patients supports the view that TSC aneurysms arise from developmental defects in the arterial wall rather than from atherosclerosis [28]. A careful pathological study of such aneurysms should be helpful in delineating the defect and in assessing the relationships between TSC-associated aneurysm and fibromuscular dysplasia [29]. The close physical proximity of the gene for autosomal dominant polycystic kidney disease-1 (PKD1), a condition characterised by a high frequency of intracranial aneurysms, and the TSC2 gene has recently been shown to play a major role in the so-called TSC2 and PKD1 contiguous gene syndrome [35, 38, 39]. No evidence of TSC2 and PKD1 DNA deletions usually responsible for this syndrome was present in our patient. In the available literature, only two cases (Table 2, cases 2 and 14) presented with the association of intracranial aneurysm and PKD1.

The present case, even if probably affected with a “forme fruste” of the disease, fulfils the diagnostic criteria for TSC [3]. In fact, two secondary (shagreen patch and renal angiomyolipomas) and three tertiary (hypomelanotic macules, renal cysts and cerebral white matter “migration tracts”) features were present, thereby allowing a definite diagnosis of TSC. This case of TSC must be considered sporadic because of the lack of evidence of TSC in other family members. The patient’s mother was completely normal, only two hepatic (not renal) cysts were present in the father, and only one tertiary feature (hypomelanotic macule) was observed in the patient’s sister. According to Roach et al. [3], two tertiary features are required for the diagnosis of TSC.

Regarding the TSC mutation analysis, a negative PTT finding does not exclude a TSC gene defect since nonsense mutations cannot be detected by this test and only the 3’ end of the TSC1 gene has been investigated thus far [40].

The intracranial aneurysm in the present TSC patient represents the 15th reported observation. This association, not as rare as previously believed, could be explained by the tendency for TSC to produce vascular dysplasias and might suggest that aneurysms can be part of the spectrum of developmental defects in TSC. In our opinion, intracranial aneurysm can be added to the other non-primary diagnostic criteria of TSC.

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References

1. Donegani G, Grattarola FR, Wildi B (1972) Tuberous sclerosis. In: Vinken PJ, Bruyn GW (eds) *Phakomatoses. Handbook of clinical neurology*, vol 14. Elsevier, New York, pp 340–389
2. Martin N, de Broucker T, Cambier J, et al (1987) MRI evaluation of tuberous sclerosis. *Neuroradiology* 29: 437–443
3. Roach ES, Smith M, Huttenlocher P, et al (1992) Report of the diagnostic criteria committee of the national tuberous sclerosis association. *J Child Neurol* 7: 221–224
4. Barroeta S, Grinspan Bozza N (1962) Tumor de koenen sin otras manifestaciones clinicas de epilolia. *Arch Argent Derrn* 12: 290–292
5. Tsukada J, Pickren JW (1967) Carcinoma of breast and asymptomatic tuberous sclerosis. *NY State J Med* 67: 593–597
6. Maniatis TM, Fritsch EF, Sambrook J (1989) *Molecular cloning: a laboratory manual*. Cold Spring Harbor Laboratory Press, Cold Spring, NY
7. The European Chromosome 16 Tuberous Sclerosis Consortium (1993) Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell* 75: 1305–1315
8. The TSC1 Consortium (1997) Identification of the tuberous sclerosis gene on chromosome 9q34. *Science* 277: 805–808
9. Au KS, Rodriguez JA, Dobyns WB, et al (1997) Mutations and polymorphisms in the tuberous sclerosis complex gene on chromosome 16. *Hum Mutat* 9: 23–29
10. Carbonara C, Longa L, Grosso E, et al (1996) Apparent preferential loss of heterozygosity at TSC2 over TSC1 chromosomal region in tuberous sclerosis hamartomas. *Gene Chromosomes Cancer* 15: 18–25
11. Gomez MR (1988) Criteria for diagnosis. In: Gomez MR (ed) *Tuberous sclerosis*, 2nd edn. Raven Press, New York, pp 9–19
12. Atlas S (1996) Tuberous sclerosis. In: Atlas S (ed) *MRI of the brain and spine*, 2nd edn. Lippincott-Raven, New York, pp 786–790
13. Fryer AE, Chalmers A, Connor JN (1987) Evidence that the gene for tuberous sclerosis is on chromosome 9. *Lancet* 1: 659–661
14. Kandt RS, Haines JL, Smith M (1992) Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. *Nature Genet* 2: 37–41
15. Lagos JC, Gomez MR (1967) Tuberous sclerosis: reappraisal of a clinical entity. *Proc Mayo Clin* 42: 26–49
16. Nathanson N, Avnet N (1966) An unusual X-ray finding in tuberous sclerosis. *Br J Radiol* 39: 786–787
17. Green GJ (1968) The radiology of tuberous sclerosis. *Clin Radiol* 19: 135–147
18. Whitaker PH (1959) Radiological manifestations in tuberous sclerosis. *Br J Radiol* 32: 152–156
19. Komar IN, Gabrielsen TO, Holt JF (1967) Roentgenographic appearance of lumbosacral spine and pelvis in tuberous sclerosis. *Radiology* 89: 701–705
20. Brill CB, Peyster RG, Hoover ED (1985) Giant intracranial aneurysm in a child with tuberous sclerosis: CT demonstration. *J Comput Assist Tomogr* 9: 377–380
21. Sobata E, Okhuma H, Suzuki S (1988) Cerebrovascular disorders associated with non Recklinghausen's neurofibromatosis. *Neurosurgery* 22: 544–549
22. Lie JT (1991) Cardiac, pulmonary and vascular involvements in tuberous sclerosis. In: Johnson WG, Gomez MR (eds) *Tuberous sclerosis and allied disorders: clinical, cellular and molecular studies*. New York Academy of Sciences, New York, pp 58–70
23. Rolfes DB, Towbin R, Bove KE (1985) Vascular dysplasia in a child with tuberous sclerosis. *Pediatr Pathol* 3: 359–373
24. Libby PA, Maitem AN, Strauss EB (1989) Axillary artery aneurysm in a patient with tuberous sclerosis. *Pediatr Radiol* 20: 94
25. Hagood CO, Garvin DD, Lachina FM, et al (1976) Abdominal aortic aneurysm and renal hamartoma in an infant with tuberous sclerosis. *Surgery* 79: 713–715
26. Davidson S (1974) Tuberous sclerosis with fusiform aneurysms of both internal carotid arteries manifested by unilateral visual loss and papilledema. *Bull LA Neurol Soc* 39: 128–132
27. Guffman M, Tanen SM, Lambert CD (1984) Visual loss secondary to a giant aneurysm in a patient with tuberous sclerosis. *Can J Neurol Sci* 11: 472–474
28. Beall S, Delaney P (1983) Tuberous sclerosis with intracranial aneurysm. *Arch Neurol* 40: 826–827
29. Blumenkopf B, Maj MC, Huggins MJ (1985) Tuberous sclerosis and multiple intracranial aneurysms: case report. *Neurosurgery* 17: 797–800
30. Copley DJ (1985) Case of the season. *Semin Roentgenol* 22: 107–109
31. Engel U (1992) Intracranial aneurysm in concomitance with tuberous sclerosis. *Zentralbl Pathol* 138: 67–70
32. Marti Masso JF, Carrera N, Zabalza R (1983) Anomalias vasculares en un caso de escierosis tuberosa. *Neurologia* 1: 52–54
33. Spangler WJ, Cosgrove RG, Moundjian RA, Montes JL (1997) Cerebral arterial ectasia and tuberous sclerosis: case report. *Neurosurgery* 40: 191–193
34. Snowdon A (1974) Cerebral aneurysm, renal cysts and hamartomas in a case of tuberous sclerosis. *Br J Urol* 46: 583
35. Longa L, Scolari F, Brusco A, et al (1997) A large TSC2 And PKD1 gene deletion is associated with renal and extrarenal signs of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 12: 1900–1907
36. Khang Loon H (1980) Intraventricular aneurysm associated with tuberous sclerosis. *Arch Neurol* 37: 385–386
37. Yasargil MG (1984) *Microneurosurgery*, vol I. Georg Thieme, Stuttgart, p 292
38. Brook-Carter PT, Peral B, Ward CJ, et al (1994) Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic disease—a contiguous gene syndrome. *Nature Genet* 8: 328–332
39. Sampson JR, Maheshwar MM, Aspinwall R, et al (1997) Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. *Am J Hum Genet* 61: 843–851
40. Povey S, Burley MW, Attwood J, et al (1994) Two loci for tuberous sclerosis: one on gene 9q34 and one on 16p113. *Ann Hum Genet* 58: 107–127