Acta Neurol. Belg., 2010, **110**, 89-92

Tuberous sclerosis with multiple intracranial aneurysms: atypical tuberous sclerosis diagnosed in adult due to third nerve palsy

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Abstract

Association between tuberous sclerosis and intracranial aneurysms is not well established and is at best suspicious. Sporadic cases of incidentally detected unruptured single, anterior circulation aneurysms have been reported in the literature in cases of typical tuberous sclerosis. We herein describe an unrecognised case of atypical tuberous sclerosis with bilateral PCom aneurysms which was diagnosed retrospectively while evaluating an unexplained intracranial hemorrhage with third nerve palsy. We intend this case would again strengthen a possible association between TS and intracranial aneurysms and lead to a systematic larger prospective/retrospective analysis.

Key words: Tuberous sclerosis; aneurysms; renal failure; focal segmental glomerulosclerosis.

Introduction

Tuberous sclerosis (TS) is an autosomal dominant neurocutaneous syndrome. The disease is characterized by hamartomatous lesions in various organs. TS can affect both sexes and all ethnic groups. The estimated prevalence ranges from 1/6000 to 1/12000 (Baron *et al.*, 1999). About two-thirds of cases are sporadic (Narayanan, 2003). Diagnosis is usually established easily in early childhood although atypical adult presentations have occasionally been reported in literature.

Case report

A 38 year old non-diabetic, hypertensive woman presented with headache and 3rd cranial nerve palsy. She had undergone renal transplantation 10 years previously and was on long term cyclosporine therapy. Biopsy of her native kidneys had revealed focal segmental glomerulosclerosis which was presumed to be due to hypertension. She developed an increasingly severe and persistent retro-orbital headache approximately 3 weeks prior to admission, with subsequent evolution of right third cranial nerve palsy and generalized tonic-clonic seizures. Cranial CT revealed acute right medial temporal lobe hemorrhage (Fig. 1). There were multiple subependymal calcifications (Fig. 2). MRA suggested bilateral, right larger than left PCoA aneurysms. MRI revealed subependymal nodules and multiple subcortical foci of T2/FLAIR hyperintensity, many accompanied by linear T2 hyperintensity extending toward the ventricle (Fig. 3). Thorough skin evaluation revealed bilateral periungual fibromas in the upper as well as

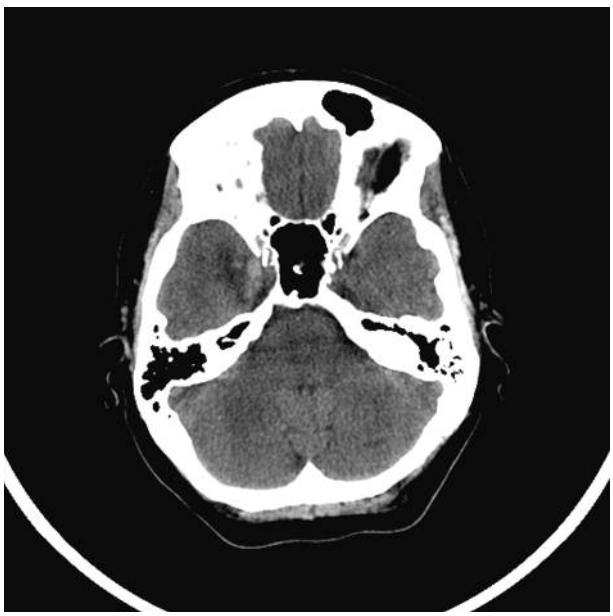

FIG. 1. — Axial unenhanced CT showing hemorrhage in the right cavernous sinus region.

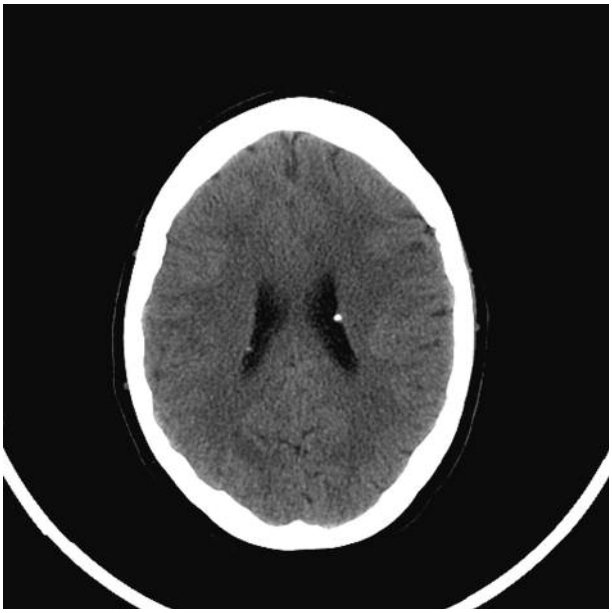

FIG. 2. — Axial unenhanced CT shows bilateral subependymal calcifications.

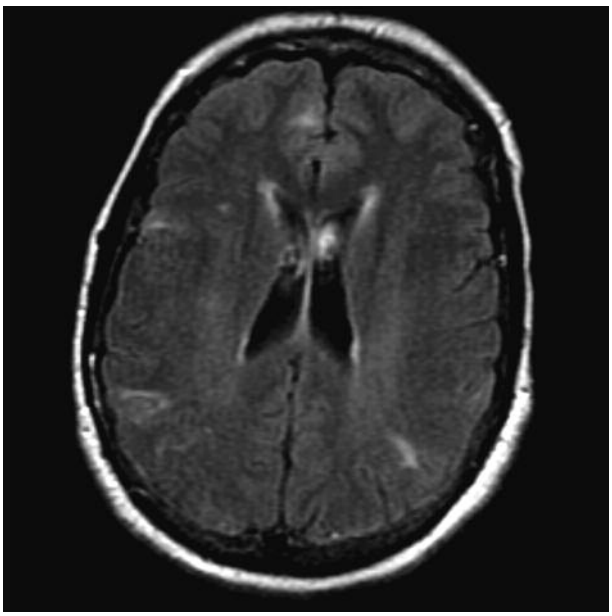

FIG. 3. — MRI with FLAIR sequence shows bilateral subcortical hyperintensities characteristic of tubers.

lower extremities and multiple hypopigmented macules on the trunk. Subsequent cranial CTA confirmed bilateral PCoA aneurysms, right larger than left (Fig. 4). A right pterional craniotomy with clipping of the right ruptured PCoA aneurysm was performed. Thorough questioning revealed a history of tuberous sclerosis in the patient's father and sister. She as well as her daughter tested positive for the

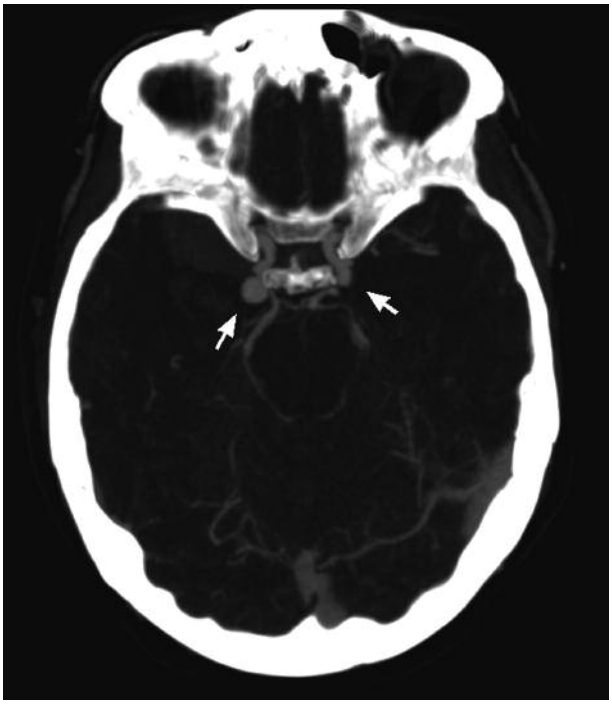

FIG. 4. — CT angiogram shows bilateral posterior communicating artery aneurysms (arrows).

TSC1 mutation. Three months later stent-assisted endovascular coiling of the left unruptured PCoA aneurysm was performed (Fig. 5). By that time her right 3rd nerve function had improved. The native kidney biopsy was revisited which did not show any angiomyolipomas but only widespread changes of focal segmental glomerulosclerosis and scattered microcysts (this is a known finding in tuberous sclerosis). Few macroscopic cysts (1-3 cms) were present in bilateral native kidneys on ultrasound which were also small and echogenic.

Discussion

Tuberous sclerosis (TS) has a variable penetrance. Mental retardation can be absent in upto 20% patients and such patients may easily escape the suspicion for TS if other findings are not very prominent. The classic triad (Vogt's triad) of epilepsy, mental retardation and adenoma sebaceum is present in upto 40% patients. Because Vogts triad may not be evident at clinical examination, radiologic examinations play an important role in the diagnosis of TS. The diagnosis is usually established on the combination of physical or radiologic findings.

Vascular lesions (stenosis, ectasia and aneurysm) are not common in tuberous sclerosis and have been found predominantly in peripheral vessels. Arterial

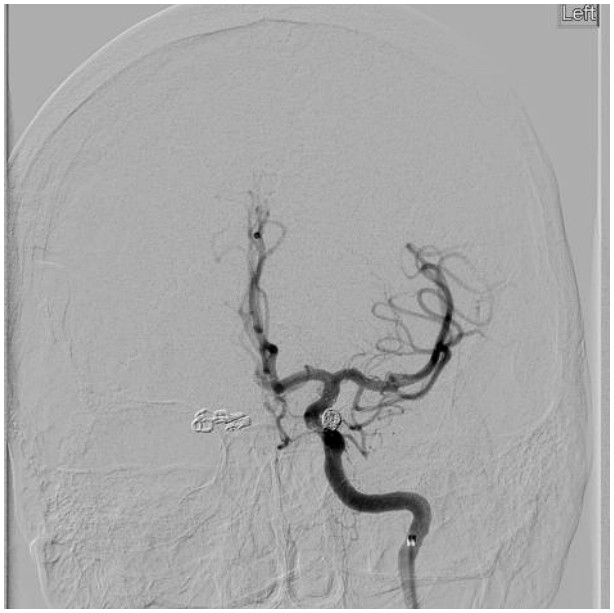

FIG. 5. — Digitally subtracted conventional angiogram shows clips over the expected location of the right and coils in the left posterior communicating artery aneurysm.

lesions previously described in TS have been mainly in the kidney, liver, aorta and distal extremities (Smulewicz *et al.*, 1997). Intracranial aneurysms are extremely rare, the internal carotid artery being the most common site of involvement. Only 16 TS patients with intracranial aneurysms have been reported. Of the 16 cases described, 6 had multiple aneurysms. The internal carotid arteries were involved in 12 of 16 cases. Five cases had anterior cerebral artery involvement and 3 cases had middle cerebral artery involvement. The age of presentation varied form 5 months to 53 years. Most of the aneurysms were incidental findings on brain imaging for other reasons (Beltramello *et al.*, 1999; Jones *et al.*, 2002). One patient died following subarachnoid hemorrhage and a ruptured saccular MCA aneurysm was discovered at autopsy (Snowdon, 1974). Two other patients presented with visual loss and papilledema (Davidson, 1974; Guffman *et al.*, 1984). Less commonly reported aneurysm locations in TS patients have included the ventricles (Khang Loon *et al.*, 1980) and vertebral arteries (Sprangler *et al.*, 1997). No TS-associated aneurysms of the PCoA origin (either unilateral nor bilateral, as seen in our case) have been described to date.

While the association of intracranial aneurysms and TS is rare and not well established, aneurysms should be carefully sought during brain imaging for TS. Timely detection and appropriate intervention can prevent the catastrophic events that complicate aneurysm rupture.

TS has been mapped to two genetic loci TS1 and TS2. TSC1 is located on chromosome 9 and encodes for the protein hamartin. TSC2 encodes for the protein tuberin, is located on chromosome 16. TSC1 and TSC2 are both tumor suppressor genes. TSC2 has been associated with a more severe form of TS than TSC1 (Dabora *et al.*, 2001). TSC2 is contiguous with PKD1, one of the genes involved in polycystic kidney disease (PKD). Deletions affecting both genes may account for the 2% of individuals with TSC who also develop PKD in childhood (Brook-Carter *et al.*, 1994). Increased incidence of aneurysms (10%) in PKD is an established fact; however such an association with TS has not been established and larger series of studies are needed to determine the same.

In our case, the astute correlation of unexplained seizures and focal segmental glomerulosclerosis might have clinched the possibility for TS. Although it might seem easy retrospectively, such high index of clinical suspicion is often difficult prospectively. Association of tuberous sclerosis with chronic renal failure had been described in literature, although rare. Most of the time it is under reported because diagnosis of TSC with renal failure is difficult when cutaneous and neurological manifestations are mild and the rarity of TSC in adults explains the lack of diagnostic experience. According to the Mayo Clinic series (Wiederholt *et al.*, 1985), after neurological involvement, renal impairment is the second cause of death in TSC (renal failure or tumoral complications, retroperitoneal haemorrhage, and metastases of renal cell carcinoma). TSC with renal failure is characterized by late diagnosis and by a predominance of females. In one series following are the frequency of renal lesions in TS – angiomyolipomas and cysts (53.8%), angiomyolipomas alone (23.1%), cysts (18.5%) and glomerulosclerosis, nephrocalcinosis (4.6%) (Schillinger *et al.,* 1996).

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