Tuberous Sclerosis Complex with an Unruptured Intracranial Aneurysm: Manifestations of Contiguous Gene Syndrome

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Summary

With the advancement of molecular genetics, the deletion of the TSC2/PKD1 gene at chromosome 16p13.3 has been discovered to be responsible for the tuberous sclerosis complex sharing some of the clinical manifestations of autosomal dominant adult polycystic kidney disease such as multiple renal cysts and intracranial aneurysms. The unruptured aneurysm in tuberous sclerosis complex is far beyond the meaning it has in general population. The risk of aneurysmal hemorrhage in tuberous sclerosis complex may be higher than that in autosomal dominant adult polycystic kidney disease due to the synergistic effect of gene deletion and certainly much higher than that in the general population. For such high-risk patients with intracranial aneurysms doomed to subarachnoid hemorrhage, magnetic resonance angiography plays an important role in screening and follow-up, especially more critically for patients with contiguous gene syndrome. Endovascular coil embolization should be the first choice of treatment for unruptured intracranial aneurysms.

Introduction

Intracranial aneurysms (ICA) have been associated with some inheritable connective-tissue disorders such as autosomal dominant

adult polycystic kidney disease (ADPKD), Ehlers-Danlos syndrome type IV, Marfan's syndrome and neurofibromatosis type I. Tuberous sclerosis complex (TSC) has been reported with ICA since 1970s¹. Recently, more and more reports show some clinical manifestations of ADPKD in TSC patients, for example, tuberous sclerosis with ICA, multiple renal and liver cysts of variable size and early onset of end-stage renal disease². With advances in molecular genetics, the TSC2/PKD1 contiguous gene syndrome has been described. TSC2 and PKD1 genes share a common location at chromosome 16p13.3. The occurrence of TSC2 and PKD1 gene deletion and the overlap of the phenotypes of TSC and ADPKD have been demonstrated³. We describe a case fulfilling the diagnostic criteria for tuberous sclerosis but with a newly developed unruptured intracranial aneurysm, and discuss the potential risk of aneurysmal hemorrhage and possible management strategy.

Case Report

A 19-year-old male had been diagnosed with tuberous sclerosis at eight years of age in 1989. He presented with two episodes of convulsions in 1986 and 1989 and the seizures were well controlled by medicine thereafter. Dermatological examination showed hypomelanotic mac-

Figure 1 Cranial MRI with T2-weighted images shows typical findings of tuberous sclerosis of multiple subependymal nodules with variable size (arrow in A and arrowheads in B). The largest one (arrow in A) near the foramen of Monro displays low signal intensity on all pulse sequences suggesting calcification. Subcortical hamartoma (double arrows in B) shows high signal intensity on the right parieto-occipital lobe.

ules and shagreen patches on limbs and trunks, and facial angiofibromas. Cranial computed tomography (CT) demonstrated multiple calcified cortical tubers and subependymal nodules. Bilateral multiple renal cysts of variable sizes were disclosed by abdominal ultrasonography. Ophthalmologic examination and auscultation of lung and heart were normal. His parents seemed well and no associated anomaly was found in his siblings or pedigree. However, the family declined further molecular gene analysis and genetic consultation. Due to mental retardation, autistic and bizarre behavior, the patient attended a special school. He suspended the medication because of absence of seizures two years later. Unfortunately, generalized tonic-clonic seizure occurred twice within a 24-hour interval in 1999 after which he started to receive regular Phenytoin control but the dose of medication had increased. Follow-up of magnetic resonance images (MRI) showed no significant change in the size of the multiple subependymal and cortical hamartomas (figure 1) but a newly developed pouch was seen arising from the right internal carotid artery, which

was proved by digital subtraction angiography to be a paraclinoid aneurysm (0.8x0.7 cm) with relative narrow neck (< 4 mm) from the right internal carotid artery (figure 2). There was no clinical or radiographic evidence of aneurysmal rupture. The patient was referred to us for further evaluation.

Discussion

Tuberous sclerosis complex or so-called Bourneville disease was first described by Vogt in 1908 as a triad of clinical features: mental retardation, epilepsy and adenoma sebaceum. However, the clinical expressions vary so that half of TSC sufferers will have normal intellect, a quarter will not have epilepsy, and almost any organ in the body can be affected⁴. Gunther and Penrose described the autosomal dominant pattern of inheritance of TSC in 1935 and recent investigations have confirmed that TSC is caused by gene mutations that affect the migration and differentiation of neural crest cells in many organs and tissues, mainly involving the brain, skin, kidneys, lung and heart^{4,5}. The

disease is estimated to have a birth incidence of 1 in 6000 and more than 70% of cases will be new mutations. Of these new mutations, it appears that 75% are caused by TSC2 mutations⁵.

There are two genes causing the TSC clinical phenotypes. TSC1 is found on the long arm of chromosome 9 and the TSC2 gene is situated on the short arm of chromosome 16. Kandt et al revealed the locus of TSC2 on the proximal side of the ADPKD type 1 (PKD1) gene on chromosome 16p13.3, only 48 base pairs of DNA from the gene for PKD1 and in tail-to-tail orientation³. ADPKD is also genetically heterogeneous, with two chromosomal loci accounting for the disease. When the mutation is located on chromosome 16p13.3, so-called PKD1 gene, extra-renal manifestations such as rupture of ICA are well known. In the case of localization on chromosome 4, PKD2 gene, the phenotype is mild and only three case reports have been associated with ICA⁶.

ICA are common. Autopsy studies have shown that the overall frequency in the general population ranges from 0.2 to 9.9% and mean frequency is approximately 5%. As compared with the incidence of aneurysmal subarachnoid hemorrhage (approximately ten cases per 100,000 persons per year), most intracranial aneurysms do not rupture^{7,8}. Considerable evidence supports the role of genetic factors in the pathogenesis of ICA. There are two main lines of evidence association with ICA: the heritable connective-tissue disorders and the familial ICA. Of the numerous heritable connective-tissue disorders that have been associated with ICA, the most important are ADPKD, Ehlers-Danlos syndrome type IV, Marfan's syndrome and neurofibromatosis type I⁷. It is not known whether the frequency of specific heritable disorders is present in the population of patients with ICA: in one series of 100 consecutive patients with ICA, five had known heritable connective-tissue disorders, but the incidence may be higher. The aneurysms in these heritable diseases are usually saccular but fusiform or dissecting aneurysms have also been described⁷. ICA are observed in about 25% of ADPKD at autopsy, and they are the cause of death in approximately 20% of ADPKD patients. Conversely, ADPKD accounts for between 2% and 7% of all patients with ICA. There was no reported association with ICA prevalence in patients with TSC and further investigation is

needed. Nevertheless, the risk of rupture of ICA in TSC patients would be higher than that in patients with ADPKD because of the clinical observation of the synergistic effect of deletion of both TSC2/PKD1 genes leading to earlier onset of polycystic kidney disease and end-stage renal failure in patients with contiguous gene syndrome³. ICA are rare in pediatric patient, only 54 cases being reported in the literature⁹. Almost always pediatric ICA occur after the first year of life. The age of ADPKD patients with ruptured ICA at their bleeding episodes ranges from 6 to 69 years. From the viewpoint of the natural history of ICA in ADPKD patients, ICA in pediatric patients with contiguous gene syndrome are not uncommon.

For an unruptured aneurysm in the general population, the International Study of Unruptured Intracranial Aneurysms (ISUIA) shows that the cumulative rate of rupture of aneurysm less than 10 mm in diameter at diagnosis is exceedingly rare (less than 0.05 percent per year)⁸. In comparison with the general population, aneurysmal rupture in ADPKD occurs at an earlier age (mean age of 41 years old) and contributes to 20% of the causes of death. In reviewing current literature on subarachnoid hemorrhage due to the rupture of an intracranial aneurysm, it is a devastating event associated with high rates of morbidity and mortality. Approximately 12 percent of patients die before receiving medical attention, 40 percent of hospitalized patients die within one month after the event, and more than one third of those who survive have major neurological deficits. In spite of diagnostic, medical, and surgical advances over the past several decades, the case fatality rate for aneurysmal subarachnoid hemorrhage has not changed⁷. Therefore, treatment of unruptured aneurysms in patients with either ADPKD or TSC is mandatory. How can the unruptured aneurysm be found and treated before occurrence of aneurysmal subarachnoid hemorrhage?

Though digital subtraction angiography remains a gold standard for detecting ICA, it is too invasive for asymptomatic patients and carries some potential risks such as mortality (less than 0.1%) and permanent neurological defect (approximately 0.5%)⁷. Magnetic resonance angiography (MRA) and helical computed tomographic angiography (CTA) are noninvasive techniques used for screening of high-risk pa-

Figure 2 A low-intensity pouch was incidentally found arising from the right internal carotid artery by T2-weighted image. Digital subtraction angiography confirmed a paraclinoid aneurysm.

tients, for example, familial SAH and ADPKD. Nowadays, MRA can detect ICA as small as 2 or 3 mm in diameter, but in prospective studies the critical size for detection is about 5 mm¹⁰. The sensitivity is estimated at 86-95% and the specificity may be up to 100%¹¹. MRA follow-up is necessary since *de novo* aneurysms develop in patients with ADPKD¹². However, MRA is insufficient for surgical planning. CTA is better in surgical planning because of its ability to demonstrate the relation of the aneurysm to the bony structures of the skull base. CTA is also useful in screening for new aneurysms in patients with initial aneurysms treated with ferromagnetic clips; these older clips are an absolute contraindication to MRA⁷.

However, radiation and contrast medium administration are major limitations of CTA, especially in patients with ADPKD and impaired renal function. Approximately five to ten percent of asymptomatic adults with ADPKD who undergo MRA screening are found to have saccular ICA¹². This screening program can also be applied to patients with contiguous gene syndrome, who potentially carry higher risk than ADPKD.

Surgical clipping and endovascular treat-

ment are two mainstays to treat ICA, either rupture or unruptured. The ISUIA demonstrated in a long-term retrospective study that the risk of morbidity and mortality related to surgery to treat unruptured ICA smaller than 10 mm is high (17.5%, greatly exceeding the 7.5-year risk of the general population)⁷. Endovascular coil embolization is a newly developed technique applied since 1990s and mostly used for obliteration of the ruptured aneurysm. The complication rate of Guglielmi detachable coils (GDC), the most popular technique, is between two and six percent. Rebleeding is rare (< 1% per year), and complete occlusion of the aneurysm can be achieved in 70%-80% of small and medium-sized aneurysms with a relatively small neck¹³. According to our experience, a 90% occlusion rate can be achieved in 83% of patients. Of 203 patients treated by GDC over five years, only one patient suffered from rebleeding because he refused complementary surgery for aneurysmal regrowth. The permanent morbidity (3.1%) and mortality (11%) are significantly lower than those of surgery and the procedure-related risk is very low¹⁴. Though endovascular coil embolization for treatment of unruptured aneurysm is a new

challenge, ICA rupture or not is of little significance in coil embolization. The major factors affecting the obliteration by coils embolization is only the ratio of aneurysmal diameter and neck⁷. Besides, endovascular treatment is less invasive than surgery because brain retraction and cranial nerve manipulation are avoided¹³.

We deduce that this adolescent patient with tuberous sclerosis, polycystic kidneys disease

and unruptured ICA had a phenotype of TSC2/PKD1 contiguous gene syndrome. He would develop earlier onset of end-stage renal disease and a higher risk of aneurysmal subarachnoid hemorrhage than the patient with ADPKD. Endovascular coil embolization is justified for the treatment of the aneurysm. MRA is necessary for follow-up to detect newly developed aneurysms in the future.

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