

A Case Report of Tuberous Sclerosis Complex (TSC) with Unilateral Retinal Phakoma

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Abstract

A 6-year-old girl was diagnosed fortuitously of a right peripapillary phakoma on routine eye consultation. This ophthalmologic lesion lead to the diagnosis of tuberous sclerosis thanks to associated skin lesions, MRI abnormalities and genetic tests. This case report showed an atypical presentation of tuberous sclerosis complex made by an ophthalmologist.

Keywords: Tuberous Sclerosis; Retinal Phakoma

Abbreviations

TSC: Tuberous Sclerosis Complex

Introduction

Tuberous sclerosis complex (TSC), also known as Bourneville's tuberous sclerosis, is an autosomal dominant phakomatosis, characterized by the development of a benign hamartoma tumor, usually located in the skin, kidney, heart, brain, and eyes [1]. We present here a case of a retinal TSC associated with skin kidney and brain lesions, in a 6-year-old girl. We will also discuss the diagnosis criteria and the specific ophthalmological signs and complications.

Case Report

We observed a 6-year-old girl on routine examination. She had no ophthalmological complaint. She had no relevant ophthalmological past. Her mother had multiple sclerosis. On ophthalmological examination, the refraction of both eyes was practiced using retinoscopy and found:

- Right eye: +1.25(-1.25)70°
- Left eye: +1.25(-0.50)95°

Visual acuity was 10/10 on the Monoyer scale, with optical correction. She had no strabism, no defense of the occlusion of any of both eyes. Stereopsis vision was normal (Lang test).

Biomicroscopic exam showed a normal anterior segment. The dilated funduscopy using indirect ophthalmoscopy with 20D lens, showed a peripapillary multinodular yellow lesion in the right eye (Figure 1a and 1b). There was no macular lesion explaining the absence of loss of vision.

The OCT showed a superficial solid formation involving the optic disc, without any exudative signs. We noticed a posterior shadowing masking the choroid (Figure 1c). The B Scan showed a calcified part of the lesion (Figure 1d).

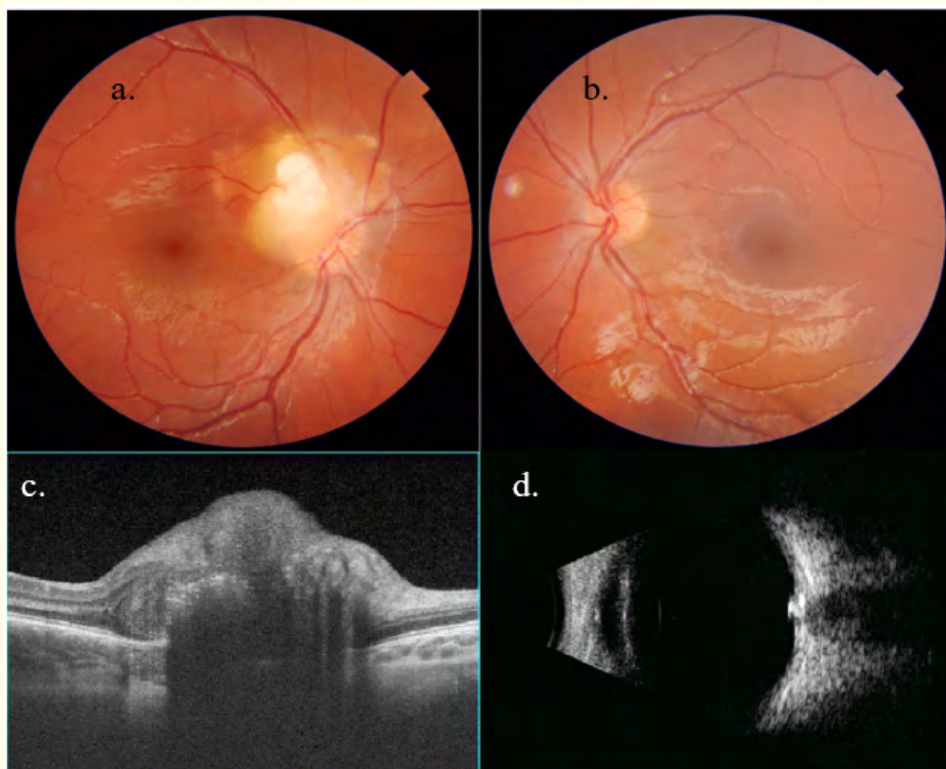


Figure 1: Retinal photographs of the right (a) and left (b) eye, OCT of the right papillae (c) and B scan (d) showing the phakoma.

Concerning systemic past history, this girl was followed by a dermatologist for white skin lesions since she was 2 years old. They were told it was vitiligo. Then, an angiofibroma of the face appeared when she was 4 years old (Figure 2a and 2b). On skin examination, she presented

- Several hypodermic skin lesions on the legs and back (Figure 2c-2e)
- Two 'cafe-au-lait' spots: in her back and around her right nipple

She has never had seizures or any neurological problems. We performed a brain MRI that found cortical tubers in the frontal and parietal lobes (Figure 3a-3c) and subependymal hamartomas (Figure 3d-3f), which confirmed the suspicion of Tuberous Sclerosis.

The echocardiography and the chest X-ray were normal. The kidney echograph suspected angiomylipoma of the cortex because of multiple hyper-reflective lesions (Figure 4a and 4b). Her glomerular filtration rate was not affected.

She underwent genetic tests and the specific biomolecular marker of TSC was found: a heterozygous variant c2743-12_2790delinsCA, on the gene TSC2. A genetic blood sample has been done on both parents to determine if it is an inherited affection or a sporadic mutation.

She had a neuropsychiatric evaluation which was normal. She had a normal psychomotor development for her age. She does theater and dance. She is at primary school and has no difficulties. She will have an electroencephalogram to avoid childhood absence epilepsy because of several episodes of headaches and dizziness.

Concerning her skin problems, she participated to a clinical trial with skin application of Everolimus (Rapamune 0,5%) 3 times a week during 6 weeks to limit the progression of the café-au-lait spots.

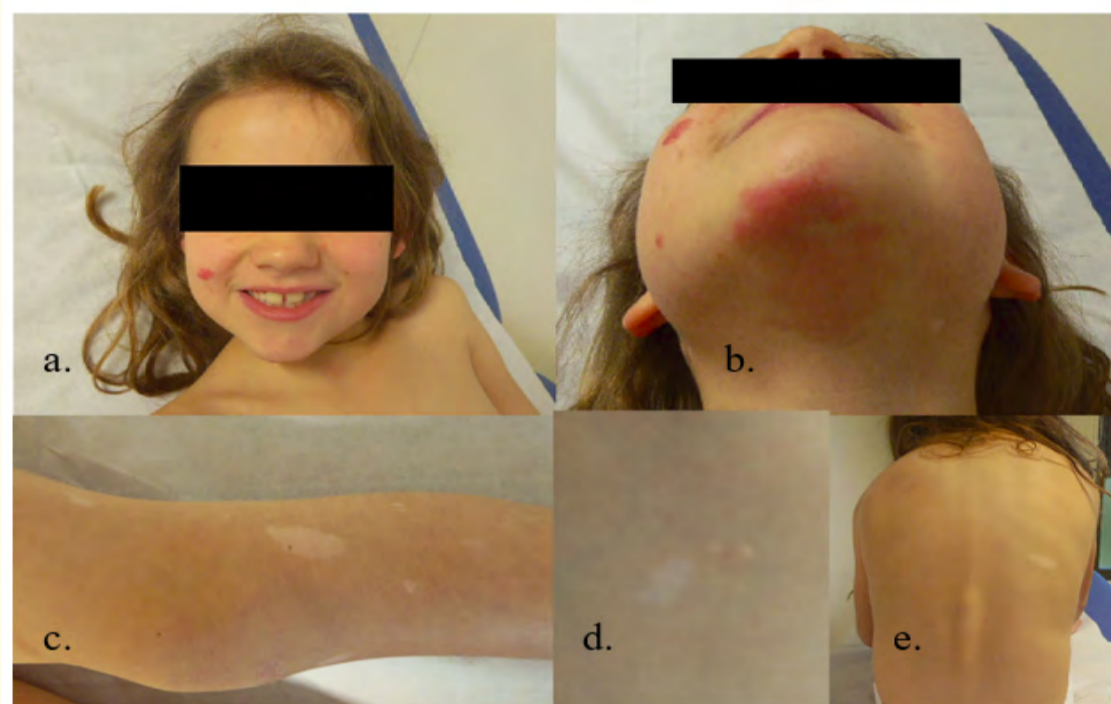


Figure 2: Angiofibroma of the face appeared at the age of 4 (a and b) and hypomelanotic macules on her leg (c) and her back (d and e).

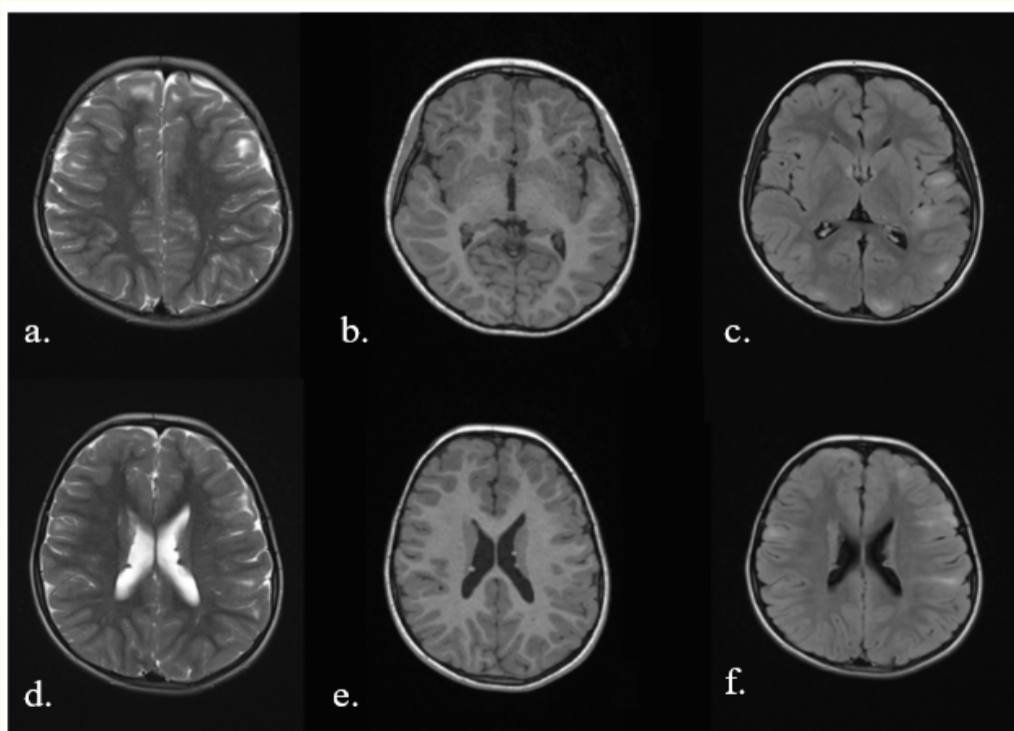


Figure 3: MRI with T2 (a), T1(b) and Flair (c) axial sequences showing tubers of the frontal and parietal lobes, and MRI with T2 (d), T1 (e) and Flair (f) axial sequences showing hamartomas of the third ventricle.

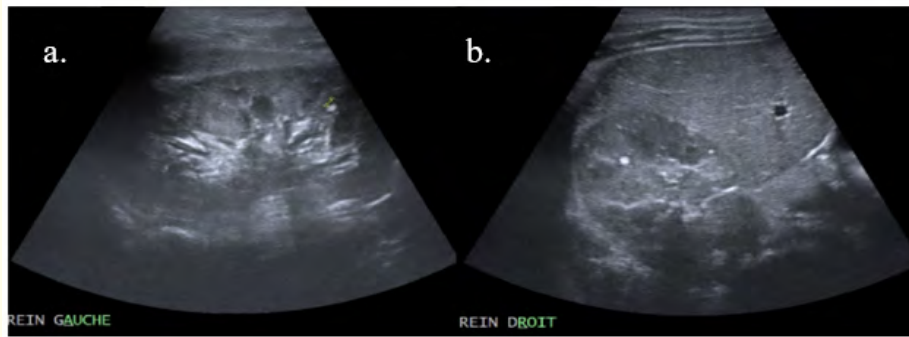


Figure 4: Left kidney (a) and right kidney (b) with the liver above with hyper reflective spots in favor of angiomyolipomas.

Results and Discussion

Tuberous sclerosis complex is a rare genetic disease due to formation of hamartomas or phakomas in the body. Phakoma is a Greek word originated from 'Phak' which means lens. Estimated prevalence is to be 1/25000 to 1/11300 and have steadily increased since its detection by Désiré Magloire Bourneville in 1880. It is still considered as a rare disease, but it is common when compared to many other genetic diseases. That's why it's important to know it.

It is an autosomal dominant inherited pathology. TSC1 and TSC2 are two tumor suppressor genes affected in TSC [2]. TSC1 encodes for the protein hamartin and is located on chromosome 9 q34. TSC2 encodes for the protein tuberlin and is located on chromosome 16 p13.3. Sixty percent of cases results from sporadic mutation. These two mutations induce indirectly an inhibition of mTor Pathway and cause a loss of control of cell growth and cell division, leading to the predisposition of forming tumors [3].

Depending of the location of the hamartomas, several physical manifestations are possible. Therefore, there are no pathognomonic symptoms. These tumors can grow in the brain and lead to seizure, intellectual disability, developmental delay, and behavioral problems. Kidneys can be affected by angiomyolipomas and causing spontaneous or post traumatic hematuria. Dermatological signs are frequently found and are part of major criteria such as: hypomelanotic macules, shagreen patches, periungual fibromas, facial angiofibromas. More rarely, some tumors can appear in the lung (lymphangiomyomatosis) and the heart (rhabdomyosarcomas) requiring a chest x-ray and an echocardiography [4].

Concerning the ophthalmological findings, we can divide them in retinal or not retinal. In the retinal findings, the first one is phakomas or astrocytic hamartomas. There are more likely next to the optic disc. Three different types are described:

- Type I: Flat, smooth, non-calcified, grey, translucent lesions
- Type II: The elevated, multinodular, calcified, opaque lesion resembling mulberries
- Type III: Both features

A new OCT classification has been done recently and found clinical features association depending on the type of hamartoma: type I and cutaneous fibrous plaques, Type II and subependymal astrocytomas, type III and lymphangiomyomatosis [5]. We can also find on the retina hyperpigmentation areas, or hypopigmentation in the posterior pole or mid periphery. Non-retinal signs include: angiofibromas of the eyelids, coloboma of the iris, lens and choroid, strabismus, poliosis of eyelashes, papilloedema, coloboma, and sector iris depigmentation.

The diagnosis is clinical. The patient must either have two or more major criteria; or one major criterion along with two or more minor criteria to conclude to a definite diagnosis of TCS; The diagnosis remains possible if the patient have either one major feature or more than two minor features [6].

Major criteria include:

- Facial angiofibroma
- Periungual fibroma
- Hypomelanotic macules
- Shagreen patches
- Cortical dysplasias (tubers and cerebral white matter radial migration lines)
- Subependymal nodules or giant cell astrocytoma
- Multiple retinal nodular hamartomas
- Cardiac rhabdomyoma
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor criteria include:

- Dental enamel pits (> 3)
- "Confetti" skin lesions, 1 - 2 mm hypomelanotic papules
- Intraoral fibromas (> 2)
- Hamartoma of the liver, spleen or other
- Retinal achromic patch
- Multiple renal cysts [6].

In our case, our patient presented four major criteria, including: facial angiofibroma, hypomelanotic macules, cortical tubers, subependymal nodules and renal angiomyolipoma. It was the identification of the ophthalmological lesion that allowed performing the diagnosis.

The ophthalmologist can be the first one to diagnoses it, without any neurological signs [7], as our example. Complications can occur like retinal detachment or exudative signs. Anti VEGF treatment or corticoids injections can be proposed [8]. It is important to rule out the different ophthalmological diagnosis of peripapillary tumors during childhood such as retinoblastoma [9], macular coats disease or neurofibromatosis.

Conclusion

The identification of a unilateral cream-white, multilobulated, well-circumscribed, elevated with "mulberry" like phakoma lead to the diagnosis of TSC because of the association with skin lesions, tuber on brain MRI and renal angiomyolipomas. Ophthalmologist can be the first to do the diagnosis. It is important to do a skin and neurological examination. We have seen this patient for two years and the lesion remains stable [10]. Fortunately, although she had several tubers and subependymal nodules, as found on the MRI, she had no neurological symptoms.

The management of this girl is multidisciplinary, involving pediatrician, neuropsychiatrist, geneticist, dermatologist and ophthalmologist. Every ophthalmologist should be aware of these signs in order to facilitate diagnosis, as we presented a case where the ophthalmologist played the main part in the diagnosis.

Conflict of Interest

No conflict of interest exists.

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