A Paediatric Case of Unilateral Ptosis Caused by Palpebral Angiofibroma Associated with Tuberous Sclerosis Complex

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Keywords

Tuberous sclerosis ; angiofibroma ; orbit ; conjunctiva ; magnetic resonance imaging ; child.

Abstract

We present an eight-year-old patient, followed since birth for unilateral ptosis of unknown aetiology, who was diagnosed with tuberous sclerosis complex (TSC) following epileptic seizures. Earlier recognition of the palpebral angiofibroma with associated ptosis might have accelerated this diagnosis. The wide phenotypic variability makes TSC a challenging diagnosis.

Introduction

Tuberous sclerosis complex (TSC) is a rare multisystem autosomal dominant genetic disorder characterized by benign and non-invasive tumours in different organs. We present the case of an eight-year-old patient who had been followed since birth for unilateral mild ptosis and swelling of the underlying temporal bulbar conjunctiva. Despite investigation by computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and orbit, aetiology remained unknown. Over time, the patient developed ipsilateral discrete telangiectatic vessels of the superior bulbar conjunctiva. At the age of eight, the patient suffered 3 epileptic insults concurrent with a COVID-19 infection. Newly performed imaging studies unravelled the diagnosis of TSC and suggested the presence of a palpebral angiofibroma next to the presumed conjunctival swelling. Only very mild other clinical signs were present. Genetic analysis revealed the presence of mutated *TSC1* (c.1257del;p.(Arg420Glyfs*20)). Earlier recognition of the palpebral angiofibroma with associated ptosis and chemosis could have accelerated the diagnosis of TSC. The wide range of clinical manifestations from mild to severe makes TSC a challenging diagnosis. Our case adds to this variable clinical picture and will hopefully aid in earlier recognition of future patients.

Case description

A 2-month-old girl presented to the Department of Ophthalmology of UZ Leuven with mild ptosis of the right eye. The girl was the second child of healthy nonconsanguineous parents. Both pregnancy and delivery went uneventful. Ophthalmological examination showed unilateral mild ptosis with swelling of the temporal bulbar conjunctiva and normal anterior and posterior eye segment appearances. Transfontanellar ultrasonography could not demonstrate any abnormalities. Preventive occlusion therapy was initiated at this time.

At 10 months of age, the conjunctival chemosis seemed clinically suggestive of a lipodermoid, for which an orbit CT scan was requested to assess for orbital involvement. The CT scan did not show a lipodermoid, but instead revealed a blurry delineated, soft tissue swelling of the upper right eyelid with infiltration of the periorbital fat without intraorbital extension, suggesting chronic periorbital cellulitis.

An MRI of the orbit was performed at one year of age to exclude lymphangioma. MRI showed a stable lesion, but the aetiology remained unknown.

The patient was examined every six months. The girl developed a minimal asymmetrical vision for which occlusion remained recommended. At the age of four years, we clinically observed a conjunctival swelling over 180 degrees, both bulbar and at the level of the plica semilunaris. Figure 1 shows photographic documentation of the clinical findings in chronological order.

At 8 years of age, the patient was admitted for a diagnostic workup of bifrontal headache and nausea. The patient tested positive for SARS-CoV-2. During hospitalization, the patient suffered 3 tonic-clonic epileptic seizures. Intravenous levetiracetam was administered and no new epileptic insults occurred. Differential diagnosis include both secondary insults due to the COVID-19 infection and primary epileptic disease. Because of persisting lateralization, an urgent MRI of the brain was performed.

The MRI findings were compatible with TSC, with additional leptomeningeal and dural contrast enhancement. Some of the cortical tubers could already be distinguished very subtly on the first MRI of the orbit performed several years earlier, which, however, did not lead to this diagnosis considering the disparate protocol regarding MRI of the orbit versus brain as well as the different focal point of the examination (eye abnormality versus neurological symptoms) (Figure 2). In addition, some subependymal nodules were also evident, another finding described in TSC.

In the following days, the patient showed a favourable evolution with recovery of lateralization and improved overall condition. She was able to leave the hospital on oral levetiracetam.

Figure 1: The first row shows clinical pictures of the patient at the age of 1 (A), 4 (B) and 6 (C) years old. The unilateral ptosis and subsequently asymmetry is evident. The second row (A'), (B'), (C') shows the conjunctival swelling most prominent temporally, at respective ages.

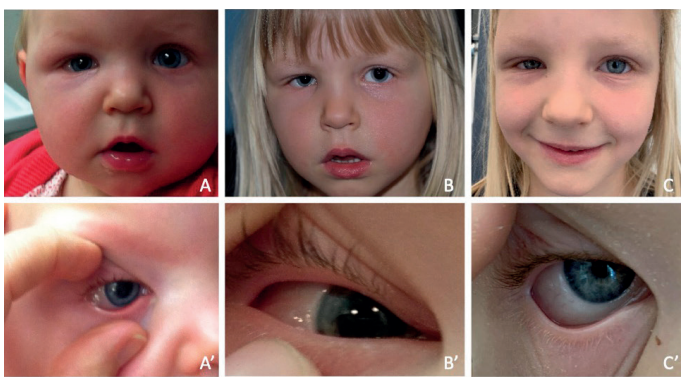


Figure 2: (A) and (B) show cerebral imaging performed by T2-weighted MRI in 2014. (A') and (B') show FLAIR images on the same levels in 2021. Some cortical tubers (arrows), intensely hyperintense in 2021, could already be distinguished very subtly in 2014 (arrows). These signs of TSC were the major clue leading to the diagnosis of a palpebral angiofibroma. (C) and (C') show respectively axial and sagittal planes of the MRI (T1-weighted with contrast) performed in 2021. The angiofibroma appears as a well-demarcated lesion in the right upper lid subcutaneous tissue with contrast enhancement due to its rich vascularization (arrows).

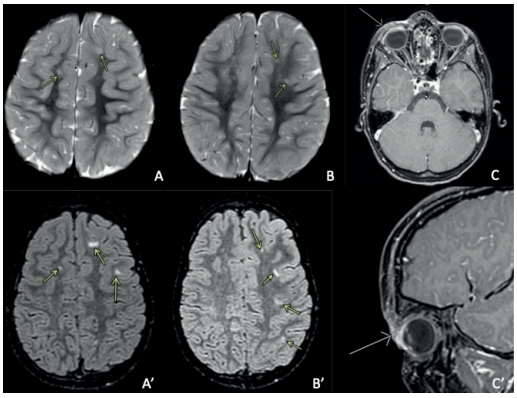
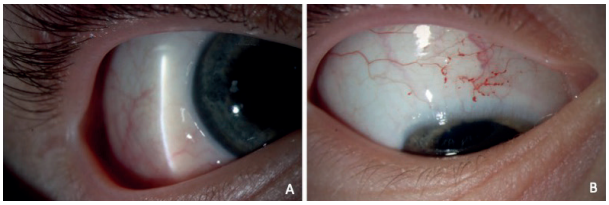


Figure 3: Clinical details through slit-lamp photography. (A) shows the angiofibroma with most prominent temporal bulbar conjunctival swelling. (B) Ipsilateral superiorly, small telangiectatic vessels of bulbar conjunctiva were observed.



Two months after admission, the patient returned for a routine ophthalmologic examination. Except for the known conjunctival swelling, we observed ipsilateral discrete telangiectatic vessels of bulbar conjunctiva, superiorly, as shown in Figure 3. A revisit of the old orbital MRI images confirmed the diagnosis of a palpebral angiofibroma next to the presumed conjunctival swelling. Dilated fundoscopic examination showed no abnormalities.

As mentioned above, TSC has a wide phenotypic diversity. This patient was on the mild end of the spectrum. Apart from a mild mathematical delay, the general development was good. Dermatologically, a low lumbar hypomelanotic patch and a shagreen patch were seen. A discrete angiofibroma was suspected on the left cheek. A limited angiomyolipoma was suspected on renal ultrasound.

Genetic analysis confirmed the presence of mutated *TSC1* (c.1257del;p.(Arg420Glyfs*20)).

Conclusion

TSC is a rare multisystem autosomal dominant genetic disorder occurring in approximately 1 in 6,000–10,000 patients. The incidence may actually be higher due to the variable penetrance and subtle clinical presentations (1). TSC is caused by inactivating mutations in the tuberous sclerosis-1 (*TSC1*) or tuberous sclerosis-2 (*TSC2*) tumour suppressor genes, resulting in hyperactivation of the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway regulates neural progenitor cell proliferation and differentiation throughout development. This causes the formation of non-cancerous tumours affecting different vital organs such as the brain, kidneys, heart, skin and eyes. TSC exhibits an extensive phenotypic diversity and clinical symptoms depend on the organs involved. The classic triad, although present only in a minority of patients, consists of seizures, mental disability and angiofibromas (1, 2). Seizures or dermatological manifestations are often the first overt clinical symptoms (1). Cerebral involvement is almost always present and represents the principal cause of morbidity and mortality (1, 3).

Retinal findings associated with TSC are hamartomas and hypopigmented macules (4). Hamartomas are present in 30 to 50 percent of the patients and are typically bilateral and multiple. These lesions do not usually cause visual impairment.

Non-retinal ophthalmological findings associated with TSC include hypopigmented sectoral lesions of the iris and ciliary body, colobomas of the iris and choroid, hamartomas of the iris and ciliary epithelium, angiofibromas of the eyelids and strabismus (2, 5). Rarely, patients may present with papilledema in the context of obstructive hydrocephalus secondary to giant cell astrocytoma (2).

With regard to neurological manifestations, a distinction was noted between *TSC1* and *TSC2*. *TSC2* mutations cause a more severe phenotype with both earlier onset and more refractory and difficult to treat seizures (1, 2). In addition, *TSC2* variants are associated with a higher incidence rate of retinal hamartomas which is the most common ocular finding (2). Patients with retinal abnormalities are more prone to develop cognitive impairment, epilepsy, renal angiomyolipoma and giant cell astrocytomas.(6)

Angiofibroma of the eyelid are the most common non-retinal finding in TSC (5). However, an ophthalmological presentation with a palpebral angiofibroma as the sole presenting sign, such as in our case, is very rare (7). Furthermore, these lesions are typically not accompanied by ptosis or conjunctival swelling. We hypothesise that the conjunctival swelling is caused by i) mechanical pressure with increased leakage from both venous and lymphatic drainage as well as ii) leakage from the highly vascularised angiofibroma.

We present a patient with a diagnosis of TSC following epileptic seizures concurrent with COVID-19 infection. Earlier recognition of the palpebral angiofibroma with associated ptosis could have accelerated the diagnosis of TSC. The extensive phenotypic variability may cause an important diagnostic delay and makes this disease a challenging diagnosis.

We aim to raise awareness among ophthalmologists, paediatricians and radiologists to consider the diagnosis of palpebral angiofibroma in patients with unilateral ptosis and undetermined conjunctival swelling.

Conflict of Interest

The authors received no financial support for the research, authorship, and/or publication of this article.

We hereby confirm that the authors have no conflict of interest to declare.

Ethics and Patient Consent

We confirm that Ethical Committee approval was obtained by the Ethics Committee Research UZ/KU Leuven (S67637).

We hereby confirm that the child's mother has read the case report in its entirety and approves of its publication, a written informed consent was obtained.

REFERENCES

1. Salussolia C, Klonowska K, Kwiatkowski D, Sahin M. Genetic Etiologies, Diagnosis, and Treatment of Tuberous Sclerosis Complex. Annu Rev Genomics Hum Genet. 2019;20:217–40.
2. Hodgson N, Kinori M, Goldbaum M, Robbins S. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017;45(1):81–6.
3. Northrup H, Koenig M, Pearson D, Au K. Tuberous Sclerosis Complex In M. P. Adam (Eds.) et. al. GeneReviews®. 1999.
4. Portocarrero L, Quental K, Samorano L, Oliveira Z, Rivitti-Machado M. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol. 2018;93(3):323–31.
5. Rowley S, O'Callaghan F, Osborne J. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001;85(4):420–3.
6. Aronow M, Nakagawa J, Gupta A, Traboulsi E, Singh A. Tuberous sclerosis complex: genotype/phenotype correlation of retinal findings. Ophthalmology. 2012;119(9):1917-23.
7. Lopez J, Ossandón D, Miller P, Sánchez L, Winter A. Unilateral eyelid angiofibroma with complete blepharoptosis as the presenting sign of tuberous sclerosis. J AAPOS. 2009;13(4).