Morbus Burneville: a case report and review of the literature

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Summary

Tuberous sclerosis (TS) or tuberous sclerosis complex (TSC), also known as Bourneville disease or Bourneville–Pringle disease, is an autosomal dominant disorder classically characterized by the presence of hamartomatous growths in multiple organs . A combination of symptoms may include seizures, developmental delay, behavioral problems, skin abnormalities, and lung and kidney diseases. The authors present a case of a 18 year-old female patient with a history of TS, epileptic episodes, mental retardation, and papillary formations in multiple organs located at the abdominal , axillary, cervical, facial, and genital region.

Key words: Multiple sclerosis; Angiofibroma; Fibroepithelial polyp.

Introduction

Tuberous sclerosis (TS) or tuberous sclerosis complex (TSC) is a rare, multi-system genetic disease that causes non-malignant tumors to grow in the brain and in other vital organs such as the kidneys, heart,eyes, lungs, and skin [1]. TSC is caused by a mutation of either of two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin, respectively. These proteins act as tumor growth suppressors, agents that regulate cell proliferation, and differentiation [2].

TSC1 encodes for the protein hamartin, is located on chromosome 9q34 and was discovered in 1997 [3]. TSC2 encodes for the protein tuberin, is located on chromosome 16q13.3 and was discovered in 1993[4]. TS occurs in all races and ethnic groups. The live-birth prevalence is estimated to be between ten and 16 cases per 100,000 with more than half of these cases undetected. [5]

The diagnosis of TS was established with the Vogt's triad, associated with learning disability, seizures, and facial angiofibroma. Despite all these, there are no pathognomonic clinical signs for tuberous sclerosis. Many signs are present in individuals who are healthy (although rarely), or who have another disease. A combination of signs, classified as major or minor, is required in order to establish a clinical diagnosis [6] (Tables 1 and 2).

In infants, the first clue is often the presence of seizures, delayed development or white patches on the skin. A full clinical diagnosis involves:

- Taking a personal and family history.
- Examining the skin under a Wood's lamp (hypomelanotic macules), the fingers and toes (ungual fibroma), the face (angiofibromas) and the mouth (dental pits and gingival fibromas).
- Cranial imaging with non-enhanced computed tomography (CT) or, preferably, magnetic resonance imaging (MRI) (cortical tubers and subependymal nodules).
- Renal ultrasound (angiomyolipoma or cysts).
- An echocardiogram in infants (rhabdomyoma).
- Fundoscopy (retinal nodular hamartomas or achromic patch) [7-8].

The incidence of disorders of certain organ system is variable, but neurological and renal complication are the leading causes of mortality and morbidity [9].

Case Report

The authors present a case of a 18-year-old female patient (gravida 0, para 0), with history of mental retardation, disability of communication and mobility, episodes of epileptic seizures, and multiple papillary lesions localized in the axillary, abdominal, and genital region. The histological examination concerning the lesions in the axillary and abdominal region revealed fibroepithelial hyperplasia and intense hypekeratosis and orthokeratosis (acral fibrokeratoma). The patient entered the present department with multiple papillary lesions localized in the region of the vulvar lips. All the clinical and laboratory examinations and the imaging findings as well, revealed no signs of malignancy. The patient underwent a wide excision of the lesion in the left vulvar lip. The histological examination revealed lesion filled with multiple fibroepithelial polyps resulting in the diagnosis of angiofibroma. All these aforementioned characteristics, the history of the patient, and the clinical examination composed the diagnosis of multiple sclerosis complex. The patient after two days in the present department was discharged from the hospital in good clinical condition.

Discussion

TSC is characterized by formation of hamartomas in multiple organ systems [10]. Although the majority of organs are susceptible, most patients exhibit dermatological, renal, and/or neurological manifestations [11]. More than 80% of people with TSC have central nervous system complications, such as severe and refractory seizures and autism [12]. Renal lesions are the most common lethal complication in patients with TSC [13]. Angiomyolipoma, hamartoma and renal cysts are major renal tu-

Revised manuscript accepted for publication February 1, 2013

Table 1. — *Major signs*

Head	Facial angiofibromas or forehead plaque
Fingers and toes	Non-traumatic ungual or periungual fibroma
Skin	Hypomelanotic macules
Skin	Shagreen patch (connective tissue nevus)
Brain	Cortical tuber
Brain	Subependymal nodule
Brain	Subependymal giant cell astrocytoma
Eyes	Multiple retinal nodular hamartomas
Heart	Cardiac rhabdomyoma
Lungs	Lymphangioleiomyomatosis
Kidneys	Renal angiomyolipoma

Table 2. — *Minor signs*

Teeth	Multiple randomly distributed pits in dental enamel (minor)
Rectum	Hamartomatous rectal polyps
Bones	Bone cysts
Brain	Cerebral white-matter "migration tracts"
Gums	Gingival fibromas
Liver, spleen, and other organs	Non-renal hamartoma
Eyes	Retinal achromic patch
Skin	"Confetti" skin lesions
Kidneys	Multiple renal cysts

mors associated with TSC. Multiple and bilateral angiomyolipoma are found in around 80% of adult patients and the developed tumors with abnormal or immature blood vessels cause spontaneous bleeding [13-14]. Multiple and large renal cysts often lead to end-stage renal failure with bacterial infections and severe hypertension. A few percent of TSC patients show pulmonary lymphangiomyomatosis, particularly those in premenopausal women [15].

TSC is caused by the mutation of either TSC1 or TSC2 gene which both encode for the proteins hamartin and tuberin, respectively [16]. Loss of the TSC genes is directly related to enhanced cell size, altered cell proliferation, and abnormal organogenesis.

Neurologic manifestations of TSC were first described by D. M. Bourneville in 1880 and were later associated with clinical signs by Vogt in 1908. Vogt described what is commonly known as the classic triad of symptoms in TSC: seizures, mental retardation, and adenoma sebaceum (angiofibromas) [17]. However, studies have revealed that the triad occurs in only 29% with TSC and six percent lack of all symptoms [18].

Some clinical types of TSC such as neonatal infantile spasms revealing hypopigmented macules occasionally lead to diagnosis [19]. On the contrary, some features remain entirely asymptomatic [20].

Cardiac rhabdomyomas are commonly found in patients with TSC [21]. They usually occur on ventricular and septal walls. Most of them regress spontaneously or disappear before birth or during childhood. Cardiac rhabdomyomas typically do not cause syptoms at birth [22].

Pulmonary involvement assumes the form of lymphangiomyomatosis and multinodular pneumocyte hyperplasia [23]. The cutaneous lesions as first sign of the disease must be widely excised and be sent for histological examination. Other treatment options include CO_2 laser, which provides efficient and bloodless excision of the lesion, or phenolization, which allows a better cosmetic result [24].

Recent therapies include the use of oral rapamycin to decrease the growth of the tumors associated with TSC. This may represent a major advance in therapy [25].

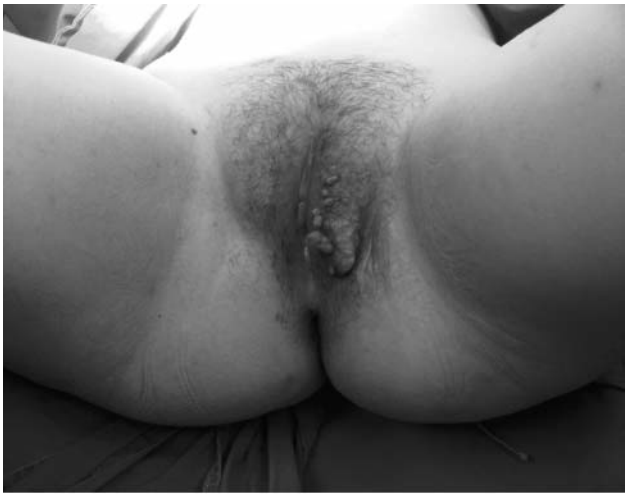

Figure 1. — Multiple angiofibromas localized in the left vulvar lip.

Conclusion

TSC is a multisystem disorder with clinical manifestations. The appropriate diagnosis requires a multidisciplinary approach to properly treat affected individuals. There is need of awareness especially of the cutaneous manifestations of the disease and of the coexistence of them with other body systems.

References

[1] Narayanan V.: "Tuberus sclerosis complex: genetics to pathogenesis". *Pediatr. Neurol.,* 2003, *29*, 404.
[2] Birchenall-Roberts M.C., Fu T., Bang D.S. Dambach M., Resau J.H. Sadowski C.L. *et al*.: "Tuberus sclerosis complex 2 gene product interacts with human SMAD proteins: a molecular link of two suppressor pathways". *J. Biol. Chem*., 2004, 11, *279*, 25605.
[3] Van Slegtenhorst M., de Hoogt R., Hermans C., Nellist M., Janssen B., Verhoef S. *et al*.: "Indentification of the tuberus sclerosis gene TSC1 on chromososme 9q34". *Science*, 1997, *277*, 805.
[4] European Chromosome 16 Tuberus Sclerosis Consortium: "Identification and characterization of the tuberus gene on chromosome 16". *Cell*, 1993, *75*, 1305.
[5] Hunt A., Lindenbaum R.: "Tuberus sclerosis: a new estimate of prevalence within the Oxford region". *J. Med. Genet*., 1989, *26*, 28.
[6] Roach E., Sparagana S.: "Diagnosis of tuberous sclerosis complex". *J. Child Neurol*., 2004, *19*, 643.

[7] Tuberous Sclerosis Fact Sheet. National Institute of Neurological Disorders and Stroke (2006-04-11). Retrieved on 2006-10-03. .
[8] Summary of Clinical guidelines for the care of patients with Tuberous Sclerosis Complex. Tuberous Sclerosis Association. April 2002.
[9] O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis complex. BJU Int. 2004;94:853-7.
[10] Crino, P.B. Nathanson K.L., Henske E.P. 2006. The tuberous sclerosis complex. N. Engl. J. Med. 355: 1345–1356.
[11] Curatolo, P., Bombardieri R., Jozwiak S. 2008. Tuberous sclerosis. *Lancet* 372: 657–668.
[12] Curatolo, P., Cusmai, R., Cortesi, F., Chiron, C., Jambaque, I., Dulac, O. (1991) Neuropsychiatric aspects of tuberous sclerosis. Ann. N Y Acad. Sci., 615, 8–16.
[13] Shepherd, C.W., Gomez, M.R., Lie, J.T. and Crowson, C.S. (1991) Causes of death in patients with tuberous sclerosis. Mayo Clin. Proc., 66, 792–796.
[14] Rakowski, S.K., Winterkorn, E.B., Paul, E., Steele, D.J., Halpern, E.F. and Thiele, E.A. (2006) Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. Kidney Int., 70, 1777–1782.
[15] Hancock, E. and Osborne, J. (2002) Lymphangioleiomyomatosis: a review of the literature. Respir. Med., 96, 1–6.
[16] The European Chromosome 16 Tuberous Sclerosis Consortium. (1993) Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell, 75, 1305–1315
[17] Curatolo P. Historical background. In: Curatolo P, ed. Tuberous Sclerosis Complex: From Basic Science to Clinical Phenotypes. London, United Kingdom: Mac Keith Press; 2003:1–10
[18] Schwartz RA, Fernandez G, Kotulska K, Jozwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. J Am Acad Dermatol. 2007;57(2): 189 –202.
[19] Jozwiak S, Schwartz RA, Janniger CK, Bielicka-Cymerman J. Usefulness of diagnosticcriteria of tuberous sclerosis complex in pediatric patients. *J Child Neurol* 2000;15(10):652– 659
[20] Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. J Child Neurol 2004;19(9):643– 649
[21] Harding CO, Pagon RA (1990). Incidence of tuberus sclerosis in patients with cardiac rhabdomyoma. Am J Genet 37: 443-446
[22] Nir A, Tajik AJ, Freeman WK, Seward JB, Offord KP, Edwards WD et al (1995). Tuberous sclerosis and cardiac rhabdomyoma. Am J Cardiol 76: 419-421
[23] Wee SA, Fangman B. Tuberous sclerosis. Dermatol Online J. 2007;13:22.
[24] Kwiatkowski DJ, Short MP. Tuberous sclerosis. Arch Dermatol. 1994;130(3):348-354.
[25] Lee N, Woodrum CL, Nobil AM, Rauktys AE, Messina MP, Dabora SL. Rapamycin weekly maintenance dosing and the potential efficacy of combination sorafenib plus rapamycin but not atorvastatin or doxycycline in tuberous sclerosis preclinical models. BMC Pharmacol. 2009;9:8.

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