Bourneville-Pringle Disease Treated with Electrocauterization and Topical Tacrolimus 0.1%: A 1 Year Observation of Severity and Recurrence

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Abstract: Bourneville-Pringle Disease (BPD) also known as tuberous sclerosis complex (TSC) is a rare autosomal dominant genodermatosis, which incidence varies from 1/12.000 to 1/14.000 live births. The genes implied to be mutated in this disease are tuberous sclerosis 1 (TSC1) and tuberous sclerosis 2 (TSC2). Diagnosis is made with two or more significant features or one major plus two or more minor features of the disorder. Management of BPD is supportive and symptomatic. Prognosis depends on systemic involvement. We reported an 11-year-old boy with various size firm tumors on his face, hypomelanotic macule on his back and slightly elevated skin-colored patch on his right lateral thigh. History of neurological manifestation and systemic complaint were adverse. Histopathological examination was following angiofibroma in BPD. Electrocauterization with general anesthesia combined with topical tacrolimus, 0.1% were performed for the angiofibromas in this patient. The prognosis was qua ad vitam dubia ad bonam, quo ad sanationam, and quo ad cosmeticam dubia ad malam. In this case, diagnose BPD was based on anamnesis, clinical features (three significant symptoms; angiofibroma, ash leaf macule, shagreen patch), and histopathological examination. The aim of angiofibroma therapy is for cosmetic purpose. Electrocauterization and topical tacrolimus 0.1% yielded a satisfactory result for the angiofibroma. Angiofibromas never worsen. There was an improvement in his FASI (Facial Angiofibroma Severity Index) score from severe to mild. Inhibitor mammalian of target rapamycin (mTOR) pathway might be considered. A proper therapy will improve a patient's quality of life.

1 INTRODUCTION

Bourneville-Pringle disease (BPD) also known as tuberous sclerosis complex (TSC) is a multisystem genetic disease with varied phenotypic expression characterized by the formation of benign tumor that very rarely develop into a metastatic lesion, on various organs like brain, lungs, skin, heart, and kidney (Darling , 2012).

BPD can affect all race and ethnic groups, regardless of gender. BPD is a genodermatosis that rarely happens with its incidence rate around 1/12,000 to 1/14,000 live births. The pathogenesis of this disease is that a mutation causes it in TSC1 or TSC2 genes lead to overactivation of mammalian target of rapamycin (mTOR) pathway, which will lead to uncontrolled cell growth (Darling, 2012; Osborne, 2011).

Definite diagnosis of BPD is made when an individual has two significant symptoms or one primary symptom with two minor symptoms (Osborne, 2011; James et al, 2011). The symptoms may vary among individuals, from mild to severe symptoms. Severe symptoms are a neurological manifestation, cardiac rhabdomyoma. Mild symptoms may include skin abnormalities such as angiofibroma, periungual fibroma, shagreen patch. Angiofibromas shows prominent vascular component owing to increased expression of angiogenic factors like vascular endothelial growth factors (VEGF) and mTOR overactivation that promotes angiogenesis. Facial angiofibromas appearance of facial papules. The diagnosis of this disease is made by taking a medical history and physical examination to form a temporary initial diagnosis (Darling, 2012; Tsao et al, 2012; Northrup et al, 2013).

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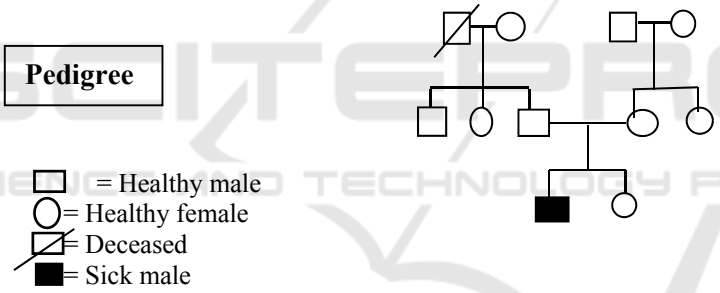
Treatment is done depending on several conditions. Some individuals with mild disease may not require treatment. Current treatment modalities include vascular laser, ablative laser and other destructive techniques such as shave excision, cryosurgery, dermabrasion, photodynamic therapy, and electrodesiccation, but that repetitive invasive techniques can cause permanent sequelae, scarring, cheloid, psychological trauma, and outcomes are often less than satisfactory (Osborne, 2011; Aoud et al, 2017; Ruano et al, 2014). The use of new topical formulations such as mTOR inhibitor and calcineurin inhibitor has recently opened up a new therapeutic perspective in the treatment of facial angiofibromas. This disease has a long-lasting effect. Even after treatment, a routine check-up is required. Children may need mental and behavioral development assessment. Early prevention can help children to grow and develop effectively (Gutreund et al, 2013; Tanaka et al, 2011).

This case aims to learn about the recent update on the diagnosis and management of BPD to improve patients' quality of life (Darling, 2012; Tsao et al,2012; Tanaka et al, 2011).

2 CASE

An 11-year-old boy patient presented to dermatology and venereology clinic of Kariadi General Hospital Semarang with lumps on his face with various size, between 0.5-2 cm in diameter, since the last six years. The lumps felt itchy occasionally, although painless and didn't bleed easily. The lumps were increasing in number and size. He also presented with a skin-colored plaque on his right thigh, 3x5 cm in size, and a painless, itchless white patch on his back, 2x3 cm in size. Now, the patient is in 1st grade of junior high class and without ever failing a grade. The patient had never undergone any treatment for his disease. History of seizure, epilepsy, and other systemic disorder was denied by the patient. The patient was delivered usually by a midwife, and there were no developmental abnormalities. History of an allergic reaction to any food or medicine was denied. History of vitiligo and cheloid was denied. However, the history of cheloid in his father was positive. Family history of the same disease was denied.



Physical examination from general state: proper, compos mentis, dermatological status of patient showed: hypopigmented macule with discrete border (ash leaf macule) on his back, 2x3 cm in size **(Figure 1.A),** skin-colored plaque (shagreen patch) on his right thigh, 3x5 cm in size **(Figure 1.B)**, multiple hyperpigmented papules and nodules on his face and nose (angiofibroma) in varying diameters, around 0.5-2 cm, FASI score 9 (severe) **(Figure 2.A)**, Laboratory result was standard.

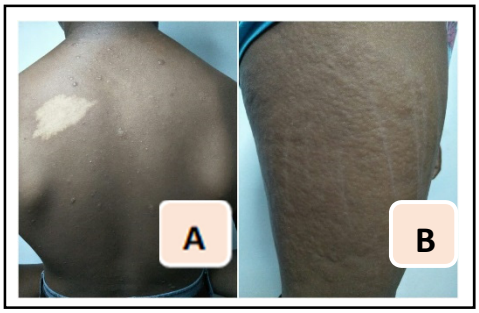


Figure 1. A. Ash leaf macule. B. Shagreen patch.

Consultation with pediatric department showed no systemic disorder. Consultation with pediatric psychology department showed an IQ test result of 95 (within standard limit). There was no systemic involvement, therefore unnecessarily EEG, MRI, ECG, USG examination.

Histopathological examination showed; angiofibroma, which is one of the many manifestations of tuberous sclerosis on the skin **(Figure 2C, 2D).**

Electrocauterization was done under general anesthesia. On seventh day post-surgery, we found skin erosion, excoriation, and crust on the wound**.** The patient was educated to apply sunscreen and wear a mask when going out. In the next follow-up, 30th-day post-surgery, we found hypopigmented macule on the surgical area. In the follow-up, 180th-day post-surgery, we did not find any hypopigmented macule. After one year observation, angiofibromas on his face grew up in the form of papules, then we applied tacrolimus ointment 0.1% twice daily, educated to wear sunscreen, and educated burning sensation as a side effect of tacrolimus. After one month therapy with topical tacrolimus; erythema reduced and the angiofibroma never worsen. In this case, FASI score after therapy was 3 (Mild) **(Figure 2B).** Prognosis in this patient was quo ad vitam dubia ad bonam, quo ad sanationam, and quo ad cosmeticam dubia ad malam.

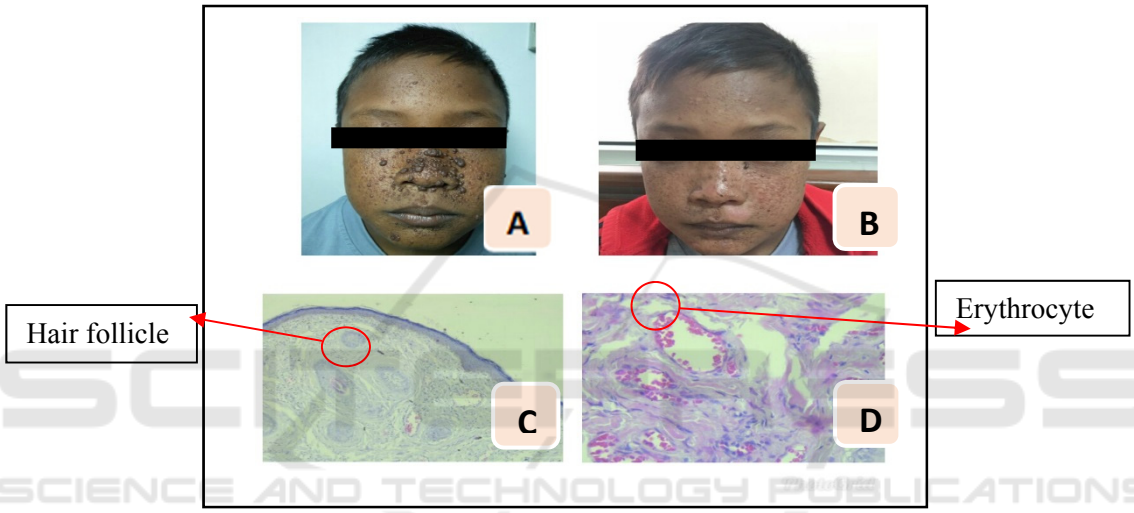


Figure 2. A. Before therapy, FASI Score 9 (severe) B. After therapy, FASI Score 3 (mild) C. 100x magnification, Epidermis; Pigmented, keratinized, stratified squamous, Dermis; Hair follicle pressed by swollen fibro collagenous connective tissue stroma D. 400x magnification, Ploriferation blood vessels coated by endothelium with lumen fulfilled by erythrocyte

3 DISCUSSION

The diagnosis of BPD, in this case, was based on medical history, physical examination, and histopathological examination. This patient met the criteria for BPD with three significant symptoms: angiofibroma, shagreen patch, and ash leaf macule. Based on US National Tuberous Sclerosis Association alliance consensus published in 2012, the diagnostic criteria of BPD consists of two significant symptoms; or one primary symptom and two minor symptoms is met **(Table 1).** (Northrup et al, 2013). Mental retardation is found in 60-70% BPD cases but if brain development during childhood is usual, mental disorder is rarely found in later life. In this patient, history of seizure was denied. The patient never failed a grade, and his IQ test result was 95 (within standard limit). (Darling, 2012;Northrup et al, 2013). Histopathological examination showed skin tissue covered by epidermis with subepithelial hyperkeratosis, fibro collagenous connective tissue stroma in which there were dilatating blood vessels, and atrophic sebaceous glands. (Tsao et al, 2012) Malignant feature wasn't found; this description fits angiofibroma found in BPD.

Differential diagnosis of trichoepithelioma can be eliminated because trichoepithelioma astarts showing in adolescence, the lesion is located on nasolabial crease, nose, forehead, upper lip, and eyelid, sometimes occurs with telangiectasis, and its peculiar histopathological feature is horn cysts. Differential diagnosis of sebaceous adenoma (SA) can be eliminated because SA usually happens in elderly, and the lesion is located on the face, head, and eyelid, histopathological examination shows irregular-shaped tumor with discrete margin, consists of lobules formed by sebaceous gland cells and basaloid. (Tsao et al, 2012)

Table 1.

major symptoms	minor symptoms
Angiofibroma	Dental enamel pits (3 or more)
Periungual fibroma (2 or more)	Intraoral fibromas (2 or more)
Hypomelanotic macules (3 or more, with the smallest diameter 5 mm)	non-renal hamartomas
Shagreen patch	Retinal achromic patch
Multiple retinal nodular hamartomas	'Confetti' skin lesions
Cortical dysplasias	Multiple renal cysts
Subependymal nodule	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis (LAM)	
Angiomyolipomas (2 or more)	

(Reference: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference)

BPD management requires a multidisciplinary approach. Generally, angiofibroma can be treated with excision, curettage, chemical peeling, cryosurgery, dermabrasion, electrosurgery, and laser. Complications that may arise from surgical treatment are an infection, hypertrophic scar, post-inflammatory hyperpigmentation, and hypopigmentation. Angiofibroma in this patient was treated by electrocauterization, curettage under general anesthesia, combined with tacrolimus 0.1%. Electrosurgery combined with topical mTOR inhibitor (sirolimus) might be a better choice to prevent recurrence of angiofibromas (Tanaka et al, 2011;Amin et al,2017) The mechanism of sirolimus binds to mTORC1 (mTORComplex1) thereby inhibiting its downstream pathway, but sirolimus is not included in the national formulary, the cost of therapy which is prohibitively expensive. We applied topical tacrolimus 0.1% in this case, mechanism of action tacrolimus is binds to a nuclear factor of activated-T cells (NFAT) to activation of genes encoding cytokines, thereby inhibiting cell cycle. We used topical tacrolimus 0.1% because it is more effective compared to the 0.03% formulation.[8] There was an improvement of FASI score from severe to mild **(Table 2)**

Table 2.

	Before therapy	After therapy
Erythema	Dark red/purple: 3	Skin color : 0
Size	Confluent : 3	<5mm : 1
Extension	>50% cheek surface: 3	<50% cheek surface: 2
Total	9	3

(Reference: 2014 British Association of Dermatologists)

FASI score is reliability assessment of new tool developed to measure severity and responsiveness to therapy in BPD-associated facial fibroma. The use of antibiotic cream was meant to prevent infection on the surgical wound. Sunscreen use when the patient went out of the house was in order to avoid direct sun exposure. (Northrup et al, 2013)

Prognosis depends on the clinical picture of the disease. Some individuals may have an average life span with few medical complications. Prognosis of this patient was qua ad vitam dubia ad bonam, quo ad sanationam and quo ad cosmeticam dubia ad malam (Darling, 2012; Osborne, 2011; James et al, 2011; Tsao et al, 2012;Amin et al,2017)

4 CONCLUSION

The diagnosis of BPD, in this case, was formed based on a patient's history, clinical picture, and histopathological examination. Clinical manifestations found in the patient were three major criteria: facial angiofibroma, hypomelanotic macule (ash leaf macule), and shagreen patch without systemic involvement. Electrocauterization combined with mTOR inhibitor (sirolimus) appears to be a promising and effective way of treating facial angiofibromas which is cosmetically disfiguring in patients with BPD. The major disadvantages are the cost of Topical Sirolimus (TS) which is prohibitively

expensive, drug preparation is not included in the national formulary, for the reason of drugs inavailability in Indonesia, we weren't able necessarily to provide topical sirolimus to the patient. Electrosurgery and Topical Tacrolimus (TT) 0.1% become the other alternatives to reduce FASI score. TT can replaces invasive procedure for angiofibroma due to tue recurrence, included in the national formulary and also cheaper than TS. TT 0.1% more effective compared to the 0.03% formulation. The severity of BPD depends on systemic involvement, while the possibility for recurrence is very high caused by TSC1 and TSC2 mutation. Therefore prognosis for this patient is qua ad vitam dubia ad bonam, quo ad sanationam, and quo ad cosmeticam dubia ad malam. Continuing observation by the doctor is important. By having proper medical management, most individuals who live with BPD can hope for a normal quality of life.

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