# EPILEPSY IN BOURNEVILLE-PRINGLE DISEASE: A CASE REPORT

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**ABSTRACT** The Bourneville-Pringle disease is an autosomal dominant neurocutaneous syndrome characterised by the formation of hamartomatous lesions in multiple organs systems. Patients develop hamartomas of the brain, kidneys, heart, lungs, skin, and eyes. Due to the wide phenotypic variability, the disease is often not recognised. This disease was classically described as presenting in childhood with a Vogt's triad of seizures, mental retardation, and cutaneous lesions. This case report provides clinicians information about the underlying disease of epilepsy. We report a case of an 18-year-old female presenting as tonic seizures and learning difficulty. The physical examination showed multiple dental pits and café-au-lait spots. An IQ test revealed moderate mental retardation. An electroencephalogram showed sharp waves in the temporal region. A head CT scan revealed cerebral oedema. A skin biopsy showed benign cutaneous tumours in the dermis consisting of Schwann cell proliferation with a wavy nucleus and fibroblast proliferation. The patient had been treated with an anti-epileptic drug. The ethiopathogenesis suggests a mutation of the two anti-oncogenes TSC1 and TSC2 which code for hamartin and tuberin proteins. The final diagnosis of this disease requires two major criteria or a major and two minor criteria, as described by Gomez. Our patient presents the major criteria of neurofibroma and two minor criteria of multiple dental pits and "confetti" skin lesions. Bourneville-Pringle disease is a rare disease. Our study has confirmed this because it is the first case seen in the Neurology department. Seizures are one clinical manifestation of this disease. Clinicians must provide a brief clinical examination in every seizure symptoms.

**KEYWORDS** Epilepsy, Seizure, Bourneville-Pringle Disease

## Introduction

Bourneville-Pringle disease, also known as Pringle-Bourneville phacomatosis, Tuberous Sclerosis (TSC) and Epiloia is an autosomal dominant genetic disease that affects multiple organ systems[1]. This disease is characterised by the formation of hamartoma lesions in the form of hyperplasia in tissues and organs such as the brain, skin, heart, kidneys, and lungs. Von Recklinghausen first described this disease in 1862 and named it Bourneville in 1880, so it was called Bourneville's disease. This disease has a wide variety of phenotypes which makes it difficult to recognise. Bourneville-Pringle disease has genetic heterogeneity; pathogenic genes contain TSC1 and TSC2 genes, which were successfully cloned in 1993. This disease occurs due to deletion, rearrangement, or an inactivation mutation of the tumour suppressor genes TSC1 or TSC2, which causes the abnormal formation of the proteins hamartin and tuberin. Both genes play a role in regulating cell growth through the phosphatidylinositol 3-kinase signalling pathway which inhibits the mammalian target of rapamycin (mTOR). This hamartin/tuberin complex play an important role in inhibiting tumour growth. These proteins suppress the activity of the mTOR pathway, which is responsible for cell proliferation and inhibition of cell apoptosis. This disease is often associated with refractory epilepsy secondary to the presence of cortical tubers, early onset of epilepsy and frequent severe seizures with declining intelligence. Effective early control of epilepsy can improve intelligence level[2,3,4,5].


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The disease affects one in 10,000 newborns and most cases are diagnosed in the first 15 months of life. This disease can affect one in 6,000 to 10,000 individuals, and it affects men, women, and all ethnicities with the same proportion. Neurological and kidney complications are the main causes of morbidity and mortality in this disease[3]. Informing the medical staff about the underlying disease in seizures is very important to reduce the morbidity and mortality rates of this disease. We hope that this case report will increase the knowledge of this disease in the medical community and provide information about appropriate treatment for patients.

## Case report

Here we present a case report for an 18-year-old female patient that came to the emergency department with status epilepticus. The patient experienced generalised tonic type seizures two times, and between the two seizures, the patient was unconscious. The seizure lasted for two minutes. The patient experienced seizures that were not preceded by fever for the first time at the age of three months. The patient saw the doctor until the age of seven years and was declared cured. The same type of seizures reappeared one year later. The seizures appeared two to three times a month and often occurred when the patient is asleep early in the morning. The patient was also said to have learning difficulties and self-care deficits since the patient was eight years old and in the second grade of elementary school. The patient dropped out of school at age 11 when she was in the fifth grade of elementary school. She also had difficulty communicating and social interactions. The patient was also said to have lumps in the left armpit and nipple. Initially, these lumps were small and then enlarged. There were no complaints of pain or itching regarding the lump. The patient was said to have brownish spots in the body area since the patient was born. She had multiple broad, brown patches of skin. Skin lesions in the form of brownish spots and bumps were also experienced by the patient. During pregnancy, the patient's mother had regular checks with a midwife. A history of drinking herbal medicine during pregnancy was denied. A history of serious illness during pregnancy was not obtained. The patient was born normal with the help of midwives with a birth weight of 2,700 grams. The patient had a history of good growth and development. This patient is the second child of two siblings whose normal brother is now 22 years old. There was no family history of seizures.

Physical examination showed an axillary temperature of 37C. Cranium and corpus vertebrae were within normal limits. The general appearance of the patient can be seen in Figure 1. There were no signs of meningeal stimulation, and other neurological examinations are within normal limits. The patient had multiple dental pits. Funduscopic examination of the patient was within normal limits. Neurofibromas were found in the anterior axillae and left nipple, and the discrete distribution in the body was accompanied by café-au-lait skin lesions. Patient's skin disorder in the form of neurofibromas with efflorescence of skin lesions in the form of nodules, round shape, size seven centimetres could be seen in Figure 2. Patient's skin disorders in the form of hyperpigmented macules such as coffee brown spots known as café-au-lait can be seen in Figure 3. Intelligence Quotient (IQ) test results were 47 (moderate mental retardation). Results of a routine hematologic examination are within normal limits. A head Computed Tomography (CT) scan showed cerebral oedema. Head CT scan, a picture of cerebral oedema in a

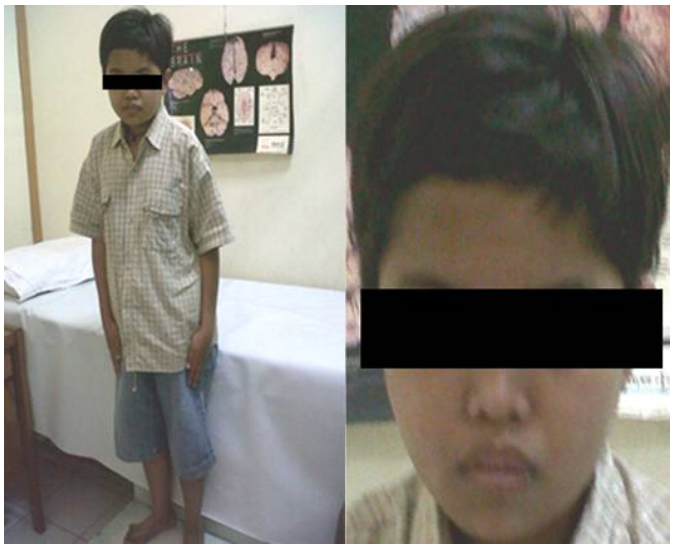

**Figure 1:** General appearance of the patient.

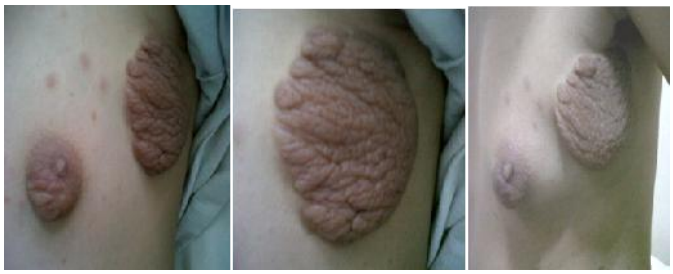

**Figure 2:** Patient's skin disorder in the form of neurofibromas: efflorescence of skin lesions in the form of nodules, round shape, size seven centimetres.

head CT scan without and with contrast can be seen in Figure 4A and 4B. The electroencephalography (EEG) recording showed abnormal results, with sharp waves in the left temporal region that can indicate potential epileptogenicity in the area. The EEG results can be seen in Figure 5. The results of the skin biopsy showed that the dermis did not have a demarcated tumour consisting of proliferation of Schwan cells with wavy core (bucket handling) and proliferation of fibrous stromal cells (fibroblasts). This skin biopsy results can be seen in Figure 6. The Bourneville-Pringle disease diagnosis was based on clinical symptoms and investigations. Treatment during seizures in the emergency unit was 10 mg of intravenous diazepam followed by intravenous 15 mg/kg body weight phenytoin at the rate of < 50 mg/min. During hospitalisation, the intravenous therapy was replaced by oral therapy of 100 mg phenytoin twice a day.

## Discussion

Bourneville-Pringle disease is an autosomal dominant genetic disease and is an important cause of epilepsy in children and adults. The diagnosis of Bourneville-Pringle disease is based on genetic and clinical criteria. Diagnosis based on genetic criteria is the identification of inactivating pathogenic mutations of the tumour suppressor genes TSC1 and TSC2. In contrast, clinical criteria include manifestations of the skin, kidneys, lungs, heart, and brain. Heinrich Vogt describes that this disease has three characteristics of epilepsy, mental retardation, and facial angiofibroma2,6. Changes in the hamartin/tuberin proteins in patients

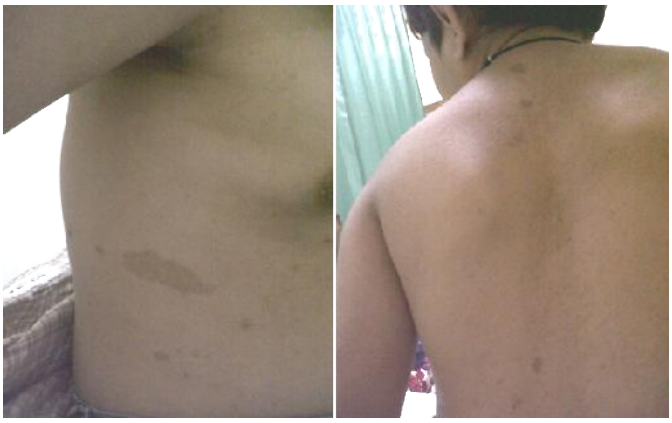

**Figure 3:** Patient's skin disorders in the form of hyperpigmented macules such as coffee brown spots known as café-au-lait.

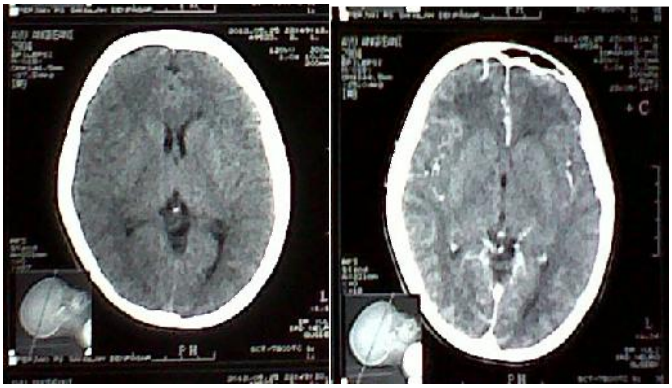

**Figure 4:** Head CT scan: a picture of cerebral oedema in a head CT scan without (Figure 4A) and with contrast (Figure 4B).

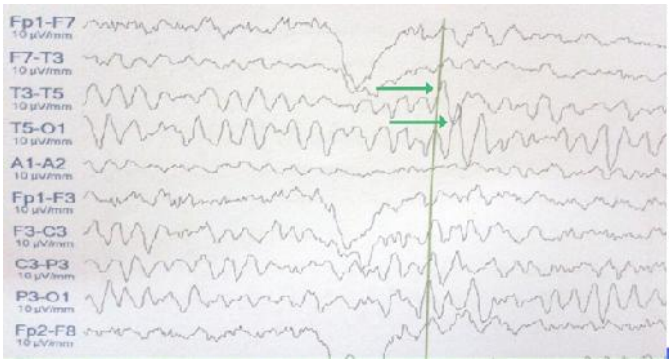


**Figure 5:** Electroencephalography results: sharp waves in the left temporal region.

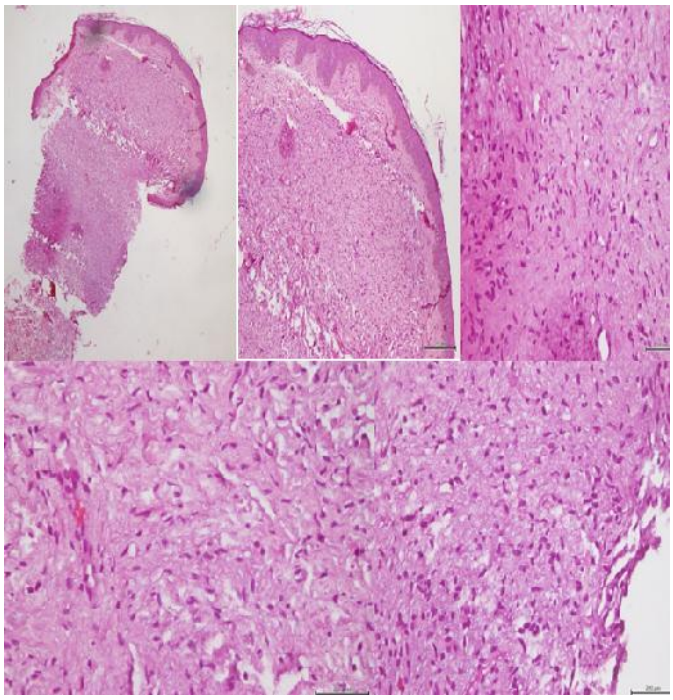

**Figure 6:** Skin biopsy results.

with Bourneville-Pringle disease cause permanent activation of the mTOR pathway, resulting in the formation of hamartomas in the organs. Cases of familial Bourneville-Pringle disease are caused by germline mutations. Although it can be hereditarily transmitted, 70% of patients are the result of somatic mutations in sporadic cases. Familial transmission cases cause mild to moderate disease and sometimes do not meet all diagnostic criteria[3,6].

Our case shows the classic triad symptoms described by Vogt, namely epilepsy, mental retardation, and skin lesions (neurofibromatosis). This classic triad is only found in 25% of patients of Bourneville-Pringle disease. Most patients affected by this disease seek medical help due to seizures and skin lesions. Both sexes can be affected by this disease in the same proportion, but women can have more skin lesions than men, although there are some individuals who suffer from this disease without skin lesions. Skin lesions can occur at any age and affect more than 90% of patients. Of all the skin manifestations in this disease, skin lesions in the form of hypopigmented macules that occur in 90% of cases and usually appear early in birth, making it easy to make a suspected diagnosis of this disease. This skin lesion resembles the shape of a leaf, rounded at one end with the other end tapering so it is called "ash-leaf". In general, the size of the skin lesions is more than five millimetres. After a few years new macules may appear smaller, round in shape, in the form of hypopigmented macules called "confetti" lesions. In adulthood, "confetti" skin lesions tend to be lighter, hyperpigmented, and may even disappear. Other skin lesions may include facial angiofibromas, connective tissue nevi, ungula fibroma, or Koenen tumour. The most common abnormality in the cavum oris are pits on the teeth enamel and gingival fibromas. Dental pits are more common in people with Bourneville-Pringle disease than in the general population, and a thorough clinical examination is needed to confirm the diagnosis. The most common skin disorder is sebaceum adenoma on the face, followed by fibroma that occurs at the age of 1-4 years, and is present in 1/3 of patients

aged two years. A history of the same disease is also experienced by mothers of the patients[1,3,5,7].

The main neurological manifestation is epilepsy. Epilepsy occurs in 70-90% of cases. Seizures usually begin in the first three years of life in the form of infantile spasms and focal seizures. All forms of seizures can occur in people with Bourneville-Pringle disease and two thirds of cases experience focal refractory epilepsy. The type of seizure in people with Bourneville-Pringle disease is not specific. When arising in older children, it can be in the form of tonic, clonic, tonic-clonic, myoclonic, or partial complex seizures. In our case, the patient firstly came with a complaint of frequent seizures. The seizures occurred throughout the body, were tonic, and accompanied by loss of consciousness. The seizure lasted one to two minutes, two to three times a month, so it was included in the criteria for epilepsy[1,3].

This patient has a high risk of developing neurocognitive deficits such as autism, mental retardation, and mood disturbances. Autism patients can be identified in 40-50% of cases. There is a prevalence of 75% of coexisting cognitive impairment and an additional prevalence of 75% to 100% of combined epilepsy. The term tuberous sclerosis-associated neuropsychiatric disorders (TAND) describes the biopsychosocial difficulties in this patient. Behaviour changes can be in the form of aggressiveness, anxiety, depressive mood, sleep disorders, and learning difficulties. As many as 30-40% of cases experience changes in neurodevelopment such as attention deficit and hyperactivity[3,8]. In our case, the patient was less able to take lessons in school. Intelligence Quotient examination results obtained moderate mental retardation. Mental deficiency in people with Bourneville-Pringle disease occurs in about 60-70% of cases.

Laboratory tests in patients with Bourneville-Pringle disease are not specific. This examination is carried out to find out early on whether there are abnormalities in the kidney, liver, heart, electrolyte abnormalities, and blood gas analysis. Our case shows that laboratory results are within normal limits[5].

Electroencephalography examination on the patient with Bourneville-Pringle disease does not show a specific picture; some cases even found the EEG within normal limits. An EEG picture can be hypsarrhythmia in infantile spasm, slow spike activity and general wave or independent multifocal spike in the adult patient[9,10]. In our case, the EEG recording shows abnormal results, i.e. sharp waves in the left temporal region could indicate potential epileptogenicity in this area.

Neuroimaging studies, head CT scan or Magnetic Resonance Imaging (MRI) examination in Bourneville-Pringle disease shows the presence of one or more calcified nodules in the lateral ventricle (subependymal nodules). The configuration and weight of the brain are usually normal. There is a sclerotic tuberal area, which can be located anywhere in the cerebral hemisphere. Head CT scans for patients with Bourneville-Pringle disease show cortical dysplasia which is characterised by the presence of cortical and subcortical tubers and migration lines in the white matter. As many as 80% of asymptomatic cases show subependymal nodules in the lateral ventricles and third ventricle, whereas 5-15% of cases with high levels of morbidity and mortality showed giant cell subependymal astrocytomas that can cause ventriculomegaly and hydrocephalus[3,7,11,12]. Head CT scan results of our case show cerebral oedema.

The diagnosis criteria for Bourneville-Pringle disease were revised in 2012. The new diagnostic criteria include genetic examination, improvement of clinical criteria, and exclusion of probable diagnosis. Based on the new criteria, identification of the pathogenic mutation in TSC1 or TSC2 DNA is sufficient to establish a definitive diagnosis. Molecular testing shows positive results in 75-90% of cases. Conventional genetic testing cannot identify a pathogenic mutation. Because of this normal results do not necessarily exclude the existence of this disease. If the patient is identified as having a gene mutation, genetic examination in other family members has a high predictive value. Clinical criteria can be used to establish a diagnosis in countries where sophisticated gene mutation analysis is not yet available. Clinical criteria are divided into major: more than two hypopigmented macules, with at least five millimetres diameter, more than two angiofibromas or fibrous cephalic plaque, more than one ungual fibromas, shagreen patches, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, more than one angiomyolipomas; and minor: "confetti" skin lesion, more than three enamel/dental pits, more than one intraoral fibroma, retinal hypopigmented macule, multiple renal cysts, and nonrenal hamartomas. Clinical definitive diagnosis is based on the presence of two major criteria or one major criterion plus two minor criteria. A probable diagnosis is made if there is one major criteria or one minor criterion. At the same time, a possible diagnosis is made if only one major criterion is found or only two or more minor criteria[3,6,7,11,13,14]. Based on the case description above, the diagnosis of Bourneville-Pringle disease in our case is based on one major criterion, namely nontraumatic neurofibromas, and two minor criteria in the form of multiple dental pits and "confetti" shaped skin lesions.

Bourneville-Pringle disease is said to be a heredofamilial and autosomal dominant disease. However, only one-third of the disease is hereditary, while the rest is due to gene mutations in the patient's own body. New mutations can occur in ovum or sperm cells. The genes involved are chromosome 9q34 (TSC1) and chromosome 16p13 (TSC2). Hamartin is a gene product for TSC1 and tuber is a gene product for TSC2, both of which interact to suppress the growth and function of cells as tumour suppressor proteins. In Bourneville-Pringle disease, they are inactivated by mutations. Abnormalities that occur in Bourneville-Pringle disease are mutations from the long arm of chromosome 9 and the short arm of chromosome 16. Gene mutations can occur spontaneously (molecular damage) or can be induction mutations caused by mutagens such as chemicals, radiation, and viral infections. In our case, the mother of the patient was found to suffer from a skin disorder similar to the patient. Both parents work as farmers and are exposed to chemical pesticides. In this case, the Bourneville-Pringle disease that occurs is most likely due to hereditary factors but further investigation is needed. Historical exploration in three generations is required for disease exploration[3,12,14,15].

The principle management of Bourneville-Pringle disease is the management of symptoms due to hamartoma lesions and prevention of organ failure. A multidisciplinary approach is strongly recommended to gain better clinical outcomes. Treatment of skin lesions can be in the form of multiple descriptive or surgical treatments such as dermabrasion to eliminate or reduce the development of facial angiofibromas, surgical excision, electrocautery, and laser removal. All these actions may cause discomfort to the patient and need repetition to prevent the recurrence of skin lesions. In this case, excision of skin lesions was not carried out at the request of the patient and her family. Early seizure control can prevent brain damage, encephalopathy that occurs secondary to epilepsy, behavioural and cognitive

deficits[2,3,15,16,17]. The management of Bourneville-Pringle disease is only symptomatic. Anti-epileptic drugs are used to treat the seizures that occur. In our case, the treatment during seizures in the emergency unit were 10 mg of intravenous diazepam followed by 15 mg/kg body weight of intravenous phenytoin at a rate of < 50 mg/min. During hospitalisation, the intravenous therapy was replaced by oral therapy of 100 mg phenytoin twice a day.

The discovery of the regulation of the mTOR pathway in the pathogenesis of Bourneville-Pringle disease and the development of target therapy using mTORC1 inhibitors provides an opportunity for patients to get improvement for the progression of their disease according to their physiopathogenesis. Rapamycin is a natural macrolide which was isolated from Streptomyces hygroscopicus in 1965. Rapamycin binds specifically to mTOR, thus causing inhibition of mTOR activity and ultimately promoting the inhibition of cellular growth. The effectiveness of mTORC1 inhibitors and derivatives of Everolimus has been tested since 2006 and has been shown to be effective in patients with multiple tumours and has a secondary benefit in patients with skin manifestations[3,15,16,17]. In our case, we did not use this therapy due to problems with the availability of this drug in Indonesia, especially in Bali. The problems that usually arise are social problems that are also experienced by the parents, for example, feelings of guilt, worry about the child's future, handling children for life, difficulty in predicting the next Bourneville-Pringle disease event, and the difficulty facing children with serious physical and mental health problems. The important thing about handling patient's with Bourneville-Pringle disease is counselling, both genetic counselling and counselling about how the quality of life for the children's future. Some patients with Bourneville-Pringle disease have normal intellectuality and live a normal life. Life expectancy for Bourneville-Pringle disease patient is good despite having severe learning difficulties or epilepsy. Some children show delays in mental development which are increasingly visible as they grow into adults. Early intervention programs for children with mental retardation can help children with Bourneville-Pringle disease. Good communication with parents of patients is needed as early as possible. Family genetic counselling is also essential to do. Genetic counselling can be done by medical geneticists or genetic counsellors. In this case, genetic counselling was given to the parents of the patient, and it was explained that this disease is a disease that can be inherited, and it is autosomal dominant. Pregnant Bourneville-Pringle disease patients should undergo chorionic villus examination in the first trimester for fetus molecular genetic testing. Genetic testing is now possible in many countries. But genetic testing cannot always confirm the diagnosis of Bourneville-Pringle disease. This test can detect mutations that occur in the TSC1 and TSC2 genes in 80% of patient with this disease. If one parent suffers from Bourneville-Pringle disease, their child has a 50% chance of getting the same disease. In unaffected parents with one child with Bourneville-Pringle disease, the likelihood of having a child with the same symptoms is one to two percent. It is necessary to form a group of patients or care for Bourneville-Pringle disease, which can be a centre of information for patients and families if there are problems related to this disease. This group is needed to support patients of Bourneville-Pringle disease and their families so that they do not feel excluded and can share information about this disease6.[12,15].

## Conclusion

Bourneville-Pringle disease is a rare disease. Our study has confirmed this because this is the first case seen in the Neurology department. Seizures are one clinical manifestation of this disease. Clinicians must provide a brief clinical examination in every seizure symptoms.

## Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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