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Case Report

Challenges of siblings with tuberous sclerosis showing various manifestations and severe complications ☆

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ABSTRACT

Tuberous Sclerosis Complex (TSC) is a rare genetic disorder that primarily affects the central nervous system and various body organs. This case series describes the case history of 2 siblings from the same parents who were diagnosed with TSC. Case 1 is a 13-year-old girl with bilateral renal AML (angiomyolipoma), multiple fat nodules in the liver, and subependymal nodules with tubers revealed in the brain magnetic resonance imaging (MRI). Case 2 is her brother, a 6-year-old boy, who presented with manifestations of subependymal giant cell astrocytoma (SEGA) and renal AML. TSC must be managed with early diagnosis and intervention due to the risk of hamartoma enlargement. These 2 cases found in siblings underline the varied clinical presentations of TSC and the complexities faced by families with TSC. Early diagnosis is important to avoid TSC-related complications because, as time goes by, the disease will impact the patient's quality of life and increase morbidity and mortality. This case series also highlights the advantages of dermatological screening for the early detection of TSC, family screening, the need for multiple imaging modalities and counseling of family members with TSC, as well as the need for ongoing follow-up of this rare disorder.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder caused by mutations in 1 of 2 genes: TSC1 or TSC2. The disease was found by Bourneville, a French neurologist, in 1880. TSC is part of a neurocutaneous disorder named *Phacomatosis*, which is derived from the embryological neuroectoderm.

TSC is characterized by the formation of noncancerous tumors or hamartomas in multiple organs including the brain, heart, kidneys, skin, lungs, and liver. These tumors can lead to a variety of symptoms and complications, depending on the location and size of the growths [1].

The incidence of TSC has been estimated as occurring in 1/5000–10,000 newborns in the world population. Therefore, this disease is categorized as a rare disease. However, TSC can often go unrecognized or may be misdiagnosed; so not all cases may receive adequate treatment.

Although TSC can occur sporadically, it can also be inherited from a parent. It has an autosomal-dominant pattern of inheritance. Therefore, a parent with a TSC gene mutation has a 50% chance of passing it on to their children. In cases where TSC is inherited, it is rarely reported in literature, especially in Indonesia.

There were no epidemiologic data regarding TSC in Indonesia, even though a few cases of spread from other provinces had been reported. But as far as we know, there have been no reported cases of siblings with TSC. In this case review, we present 2 siblings of the same parents, who were diagnosed with TSC at different times. They were presenting multi-organ symptoms that need careful consideration and integrated management to improve their quality of life.

Case illustration

Case 1

A 13-year-old girl was referred to our hospital with persistent gross hematuria, pain in the right flank, and pain during micturition. Previous history reported that she had an unknown mass in the right kidney. An emergency suprapubic puncture was performed, which revealed blood clots in the bladder. Physical examination revealed pain in the suprapubic region and right flank. Laboratory results showed anemia and low hematocrit count, with elevated SGOT and SGPT values and leukocytosis.

Some imaging modalities were performed. Abdominal ultrasound and whole abdominal CT scan with contrast (Fig. 2) revealed bilateral nephromegaly with multiple masses at the parenchyma along with dilated renal pelvis on both sides, filled with internal debris. The abdominal CT scan further revealed multiple hypodense lesions scattered on the renal parenchyma, of which some were fat densities and cysts. These findings suggest bilateral renal angiomyolipoma (AML). Multiple small hypodense fat density lesions in varying sizes were found scattered in all the segments of the liver, which correlated with the presentation of an increase in liver enzymes. Additional cystitis and bilateral pleural effusion were also found in the CT scan. The abdominal ultrasound revealed multiple hyperechoic lesions scattered in the liver and the kidneys (Figs. 3 and 4).

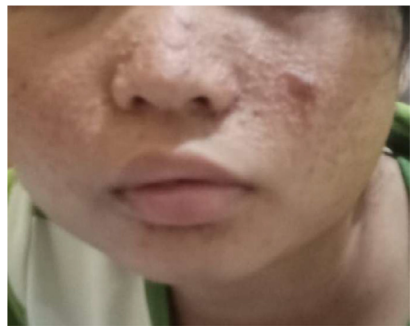

Fig. 1 – Dermatologic symptom of facial angiofibroma, hyperpigmented patches, hypomelanotic macules, and vesicles.

Physical examination showed signs of facial angiofibroma, hypomelanotic macules, hyperpigmented patches, and vesicles (Fig. 1).

This patient also had a history of epilepsy or seizures since she was six years old. A brain MRI performed with gadoteric acid contrast revealed multiple subependymal nodules (SEN), isointense at T1, and hyperintense at T2, enhanced with contrast with a blooming artifact. The brain MRI also showed multifocal cortical-subcortical tubers as focal white matter hyperintense lesions on T2 and hyperintense with central hypointense on FLAIR, spreading at the bilateral frontal, temporal, and occipital regions.

This patient underwent a nephrectomy of the right kidney and partial nephrectomy of the left kidney, due to the size of the mass with infiltration of angiomyolipoma and owing to the complication of massive hematuria. The other pathologic findings were treated conservatively using epileptic drugs and other medications. The lung lesions were treated as tuberculosis in another hospital.

Case 2

Two years later, the girl's 6-year-old brother was referred to our hospital due to unconsciousness after having multiple seizures that lasted for about an hour. Three days earlier, he had suffered from fever and cough. Physical examination showed hypomelanotic macules in the back, hyperpigmented patches near the nasofacial area, and vesicles (Fig. 5). Laboratory results showed elevated liver enzymes (SGOT & SGPT), blood creatinine, C-reactive protein, and neutrophil count. This patient had a history of attention deficit disorder (ADHD) and behavior disorder. He was being treated routinely with epileptic drugs since 1 year before the admission.

Gd-DTPA-enhanced brain MRI demonstrated bilateral subependymal nodules (SEN) along the walls of the lateral ventricles that were isointense with gray matter on the T1 weighted image. There were multiple focal hyperintensities in the subcortical white matter of the frontal, parietal, occipital, and temporal lobes (Fig. 6). The brain MRI also revealed a well-defined isointense nodule, homogenously enhanced,

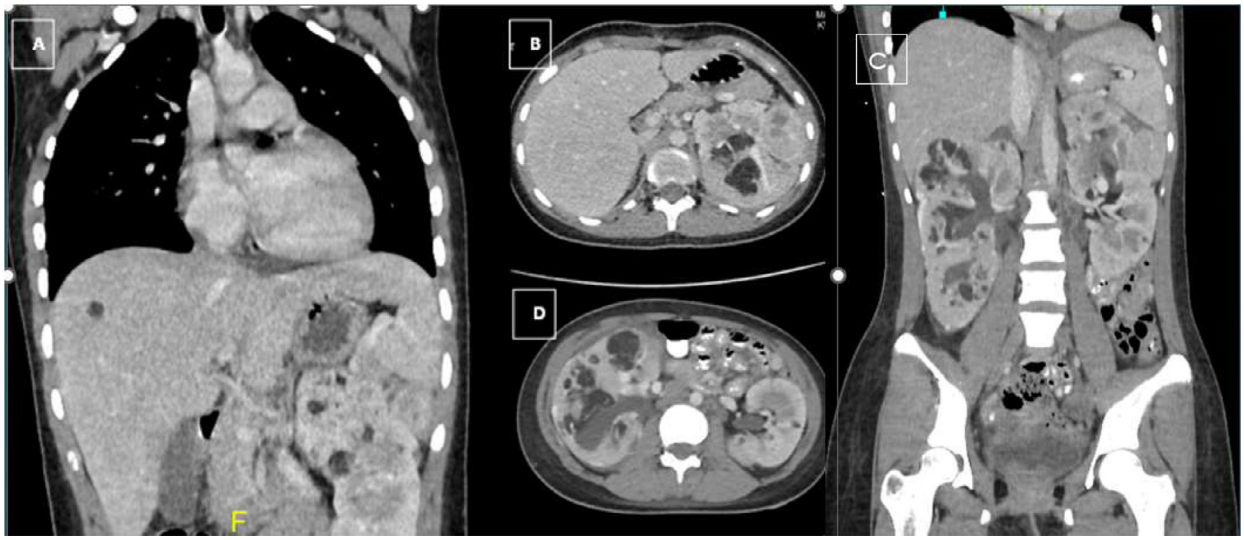

Fig. 2 – Whole abdominal CT scan showing (A) multiple hypodense lesions across different organs. In the liver, (A) hypodense lesions (HU-14) were found with the largest one measuring up to 0.8 cm. The right kidney was enlarged more than the left kidney (B–D), and both showed multiple fat and cyst components in the parenchymal tissue. Both pelvicalyceal systems were dilated and filled with mixed densities, suggesting blood clots.

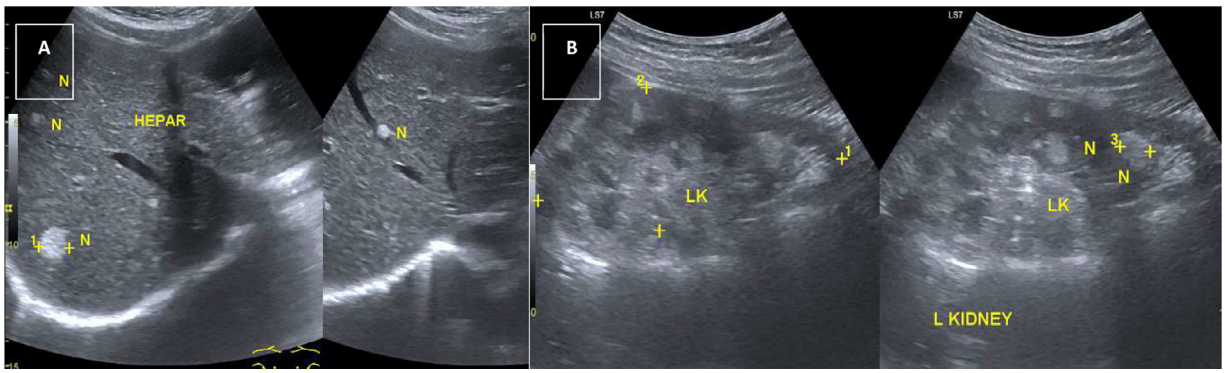

Fig. 3 – Ultrasound findings of the liver and kidneys. (A) Multiple hyperechoic lesions were found across the liver parenchyma, consisting of fat density. (B) Both kidneys showed multiple scattered hyperechoic lesions at the renal parenchyma, which can be correlated with fat nodules.

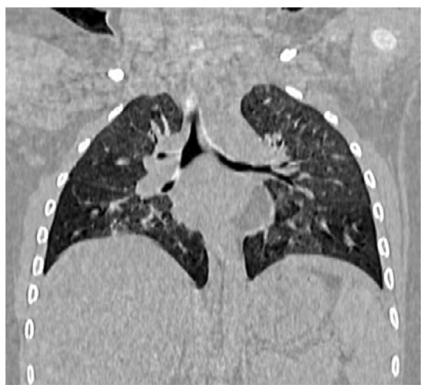

Fig. 4 – Chest CT scan showing some small hyperdense lesions scattered in both the lungs.

measuring about 1.5 × 0.9 × 1.7 cm. It was originating from the subependymal layer of the left lateral ventricle near the foramen of Monro, indicating SEGA (subependymal giant cell astrocytoma) (Fig. 7).

The abdominal ultrasound showed liver enlargement with signs of mild fatty liver and multiple small hyperechoic lesions on both kidneys, predominantly on the right kidney (Fig. 8). This was suggestive of angiomyolipoma (AML), which was confirmed in the contrast-enhanced CT scan. There were also multiple tiny cysts at the lung parenchyma (Fig. 8), suggesting LAM (lymphangioleiomyomatosis).

The patient was treated with an epileptic drug and given conservative treatment for behavior disorder and fever. He was also given symptomatic drug for cough. Since he did not have other complaints related to the findings in the brain, liver, kidneys, and lungs, conservative treatment, and follow-up for diagnosis of TSC was recommended.

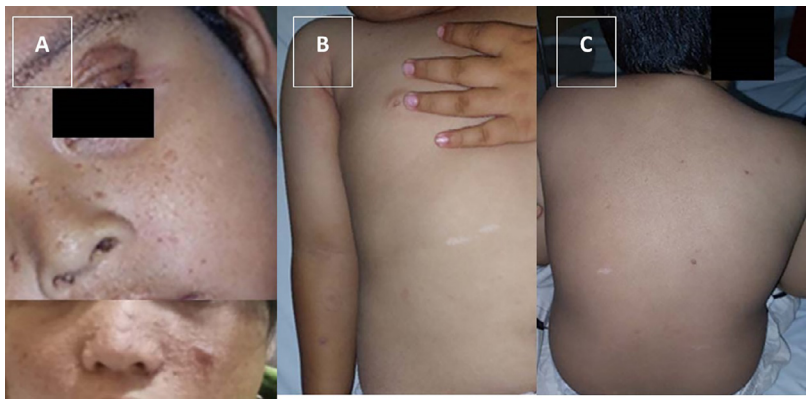

Fig. 5 – Findings from physical examination. (A) Dermatologic manifestations showing a hyperpigmented patch on the left eyelid and multiple hyperpigmented patches and plaques around the nose, suggesting facial angiofibroma. (B) Hypomelanotic macules in the skin. (C) Some vesicles on the back.

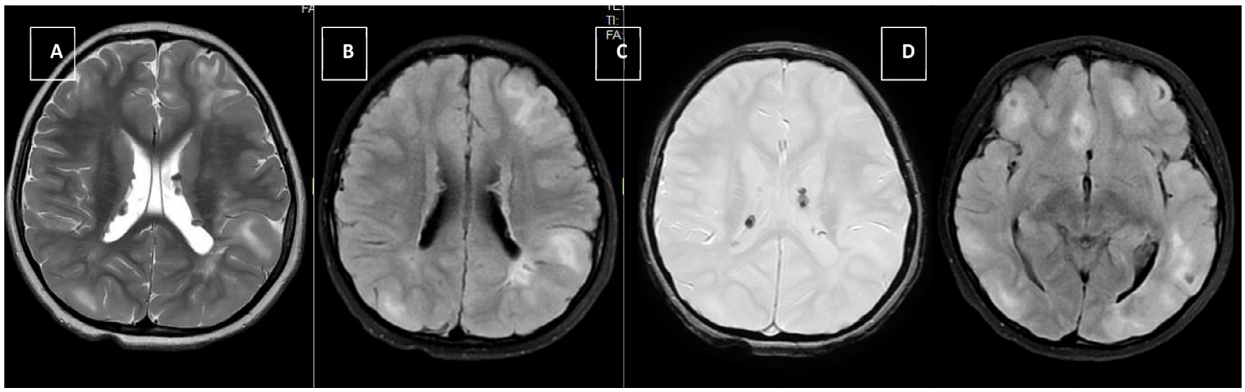

Fig. 6 – Gd-DTPA-enhanced brain MRI. (A, B, and C) Multiple subependymal nodules (SEN) at subependymal layers protruding into the adjacent ventricles, that were hypointense at T2, hyperintense at T2 Flair, and hypointense at SWI (susceptibility weighted imaging) due to calcification. (D) Multiple cortical tubers presented as focal white matter hyperintensities on T2 and hypointense at the central region, surrounded by a hyperintense rim on FLAIR, spreading at the frontal, temporal, and occipital regions bilaterally.

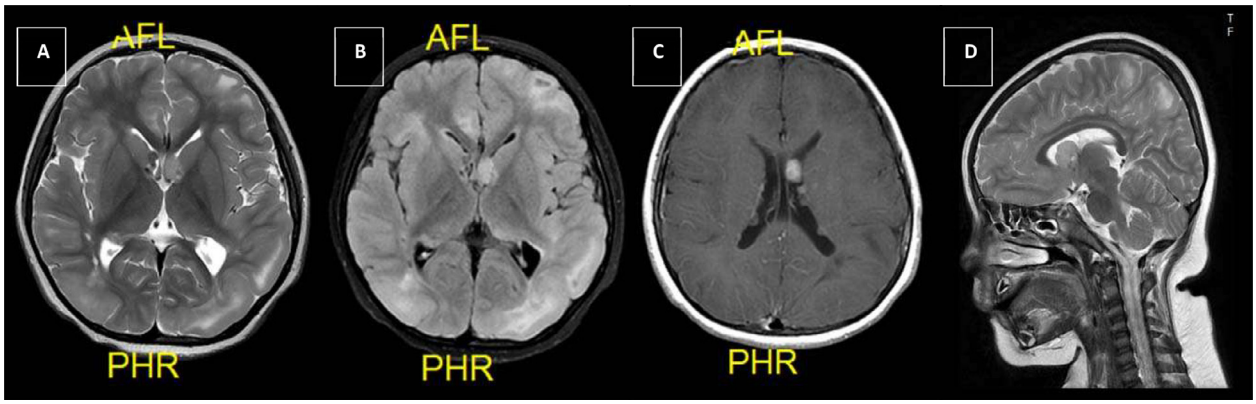

Fig. 7 – Solid nodule revealed in the brain MRI with intermediate intensity at T2 (A) and hyperintense at T2Flair (B). It was homogenously enhanced, measuring about 1.5 × 0.9 × 1.7 cm, originating from the subependymal line of the anterior horn of the left lateral ventricle and enhanced at the Gd-DTPA (C). In the sagittal view, the nodule was visibly seen at the third ventricle and identified near the foramen of Monro, which is indicative of SEGA.

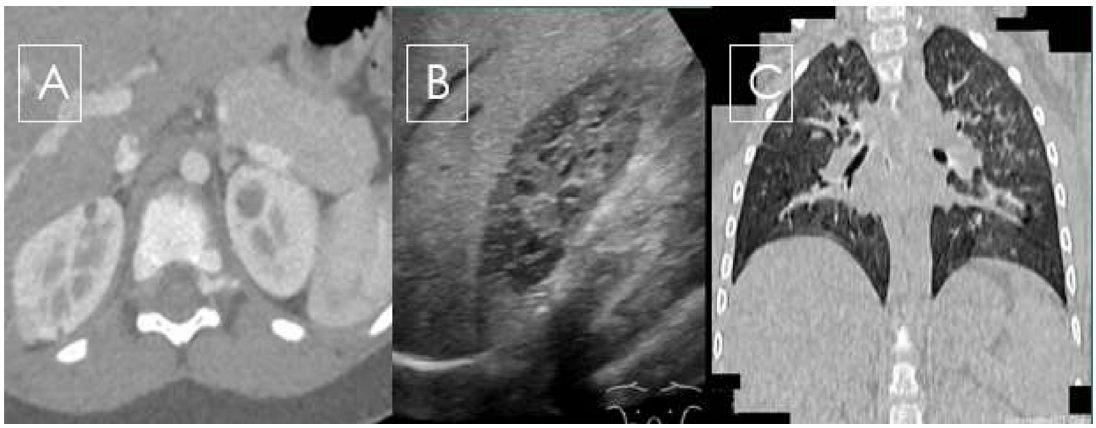

Fig. 8 – (A and B) Contrast-enhanced CT scan showing 1–2 small hypodense nodules in the kidneys. Ultrasound of the kidney showed multiple focal hyperechoic small lesions measuring less than 5mm. These lesions were spread in both the kidneys, predominantly on the right kidney, suggesting angiomyolipoma (AML). (C) Coronal chest CT scan showing multiple small, thin-walled pulmonary cysts in both lungs, suggesting LAM or MMPH of the lungs (lymphangioleiomyomatosis).

Table 1 – Major and minor features of tuberous sclerosis

Major features	Minor features
1. Facial angiofibroma or forehead plaque	1. Multiple, randomly distributed pits in dental enamel
2. Nontraumatic ungual or periungual fibroma	2. Hamartomatous rectal polyps
3. Hypomelanotic macules (three or more)	3. Bone cysts
4. Shagreen patch (connective tissue nevus)	4. Cerebral white-matter radial migration lines
5. Multiple retinal nodular hamartomas	5. Gingival fibromas
6. Cortical tubers	6. Nonrenal hamartoma
7. Subependymal nodule	7. Retinal achromic path
8. Subependymal giant cell astrocytoma	8. "Confetti" skin lesions
9. Cardiac rhabdomyoma, single or multiple	9. Multiple renal cysts
10. Lymphangiomyomatosis	
11. Renal angiomyolipoma	

Discussion

Among the different types of neurocutaneous syndrome disorders or phacomatosis, the diagnosis of TSC is made by considering major criteria and minor criteria. TSC would be a definite diagnosis if 2 major features (or) 1 major feature and 2 minor features are found in the patient. TSC would be considered probable if we found one major feature and one minor feature. TSC would be a possibility if there are 1 major or 2 minor features [2] (Table 1).

The onset and severity of clinical manifestations vary with age. This underlines the importance of early detection and treatment [3,4]. The younger brother showed 6 major features (facial angiofibroma, hypomelanotic macules, renal AML, SEN, SEGA, and cortical tubers in brain) whereas in the older sister, five major features (facial angiofibroma, hypomelanotic macules, renal AML, SEN, and cortical tubers) were observed.

Hypomelanotic macules, cortical tubers, SEN, SEGA, and renal AML were discovered in the younger brother, with 2 minor features showing up on physical examination (nonrenal hamartomas and confetti skin lesions). These features are strongly associated with a diagnosis of TSC. The younger brother also had a pathology of tiny microcysts (LAM) and micronodules (MMPH) in his lungs. According to Kaneda, LAM was found in 40% of women with TSC while MMPH was found in more than 50% of them. Although the exact prevalence of TSC in Indonesia is unknown, based on global estimates, it can be assumed that there are between 26,000 and 52,000 Indonesians who have TSC. Indonesian epidemiological data on TSC is incomplete because many cases are not detected properly, so they do not receive proper treatment.

Because TSC is a rare disease, Clinicians should be more anticipating the risk of family members developing TSC and provide counseling arrangements. In our cases, unfortunately, the clinical manifestations in these siblings emerged at different times without family awareness. The different manifestations in the 2 patients show that TSC can cause a variety of complications with a poor prognosis. The older sister had huge renal masses that she underwent a total nephrectomy in the right kidney and partial nephrectomy in the left kid-

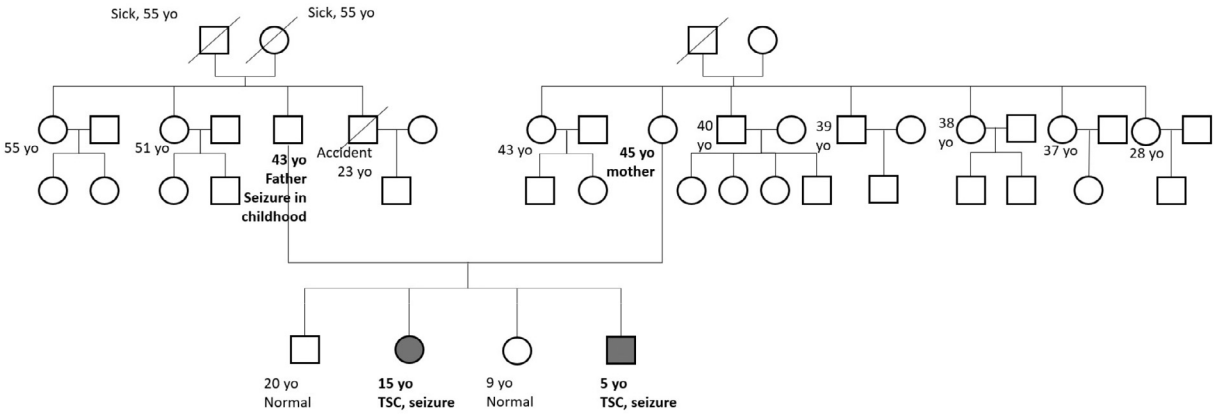

Fig. 9 – Familial history of case series.

ney due to some blood clots in the kidney, gross hematuria, and acute abdominal pain. The boy had severe seizures and his brain MRI revealed that he had developed cortical tubers and SEGA. This tumor had a risk of obstructive hydrocephalus and elevated intracranial pressure if it grew further or became enlarged, as it was located at the foramina Monroe [5]. The complexity of TSC and its diverse presentations highlight the importance of a collaborative approach between healthcare providers and parents. Parents, being closely involved in the daily lives of their children, may notice subtle changes or symptoms early on. This parental insight can serve as valuable information for family physicians or specialists in expediting the diagnostic process. We believe that recognizing the proactive role of parents can enhance the overall healthcare experience for patients with TSC.

The imaging results also showed that the boy had small renal AML and MMPH of the lungs. The siblings had a history of tuberculosis treatment in another peripheral hospital. As we did not find any signs of tuberculosis during the physical exams and microbiology findings, we thought that it could probably be a misdiagnosis of TSC in the lungs.

TSC patients who display symptoms such as seizures and neurobehavioral disorders called TAND(tuberous sclerosis-associated neuropsychiatric disorders) may require medical attention right from childhood. Others may have subtle symptoms and so remain undiagnosed until adulthood [6]. TSC is an autosomal dominant disorder that is familial in nature. Therefore, genetic testing and detection in affected families is crucial. When we interviewed this family, we realized that their father probably had genetic TSC, as he too had a history of seizures in his childhood, as shown in the family tree below (Fig. 9).

TSC disorders progress with age. Therefore, parent counseling is necessary to give the parents a chance to provide essential care and avoid their younger children from experiencing the same progression.

TSC diagnosis is based on clinical features such as multiple hamartia and hamartomas in various organs of the body. The onset and severity of clinical manifestations vary with age. Younger siblings may display the same symptoms and progressions as seen in the older sibling, especially in the kidneys. Complications of AML in the kidney can lead to renal mass and declining renal function. Malignancy of epithelioid AMLs may occur, as it is a possibility in the presence of rapid growth or necrosis [4,7–8]. Renal AMLs may appear before hepatic lesions; however, the mechanism of lesion propagation in TSC is not yet fully understood. Hepatic lesions are strongly associated with TSC2 gene mutations, as revealed by Jóźwiak S et al. (2018) [8].

Dermatological evaluation is recommended for TSC patients during the initial assessment. Hypomelanotic macules are the most common and earliest dermatologic manifestation in TSC patients, with a prevalence of 90%. They are characterized by asymmetrical distribution all over the body [4,9]. For TSC diagnosis, guidelines require a minimum of 3 hypomelanotic macules, with a diameter of >5 mm. Confetti skin lesions (found in 28% of TSC patients) can also be present [9]. While skin lesions are present in 70%-80% of TSC cases, they may remain undetected until adulthood [10].

CNS complications cause the most morbidity and mortality in TSC, affecting >80% of patients [4]. Brain CT scan and contrast MRI showed that this sibling had multiple intracranial lesions. Non-contrast CT may misinterpret calcifications at SEN as TORCH infection, but contrast MRI, in this case, depicted SEN accurately, therefore early MRI screening for TSC patients allows for earlier detection. Cortical tubers are typically benign and associated with epileptic seizures [3,4].

There is a correlation between the onset of seizure and intellectual disability; earlier onset is associated with more cognitive deficiencies [6]. TSC-associated neuropsychiatric disorders (TAND) are frequently diagnosed in TSC patients. These disorders affect not only the patient but also those around them. Therefore, TSC in families causes quite complex problems and requires high-cost long-term treatment.

The current management of TSC involves pharmacologic, symptomatic, surgical, and behavioral interventions. In newly-diagnosed or suspected TSC patients, comprehensive clinical imaging is recommended to establish a baseline status. Regular follow-up and a holistic approach are essential for minimizing morbidity and mortality. The pathologic conditions in various organ systems may lead to more complications with aging. Genetic counseling is recommended upon TSC diagnosis, as families may exhibit similar symptoms. *TSC1* mutations are more often seen in familial cases than in

sporadic new cases. Although the prognosis for this case was not good, early detection may allow better management [4,7].

Prenatal screening of TSC that may be beneficial for early intervention includes the screening of cardiac rhabdomyoma, which can be considered the initial manifestation and prenatal marker of TSC. Prenatal diagnosis of cardiac rhabdomyoma can be made with fetal echocardiography. Another prenatal screening method is by fetal MRI to detect brain malformation, the cortical tuber, which occurs in over 90% of TSC patients. Genetic testing to detect the mutation of the TSC1 or TSC2 gene can also be done by extracting genomic DNA from amniotic fluid [11].

Wang et al. emphasize the benefits of prenatal diagnosis for individuals with TSC. Prenatal screening methods include standardized check-ups and advanced imaging such as MRI and fetal echocardiogram, coupled with gene detection. Genetic testing to detect TSC1 and TSC2 can be used to strengthen TSC diagnosis. However, in developing countries like Indonesia, these tests are proven to be inaccessible to the general population due to their cost. Wang stated that preventive approach involving sirolimus and vigabatrin administration before symptoms onset can help reduce epilepsy incidence and promote better neurological development. The findings of this case suggest that preventive measures can have a significant protective effect on the development of children with TSC [4]. In a study by Katarzyna Kotulska et al., it was noted that infants who received antiepileptic treatment immediately after experiencing their first clinical seizure demonstrated better outcomes when compared to those who were treated later. The EPISTOP study showed that preventive treatment significantly lowered the risk of developing drug-resistant epilepsy when compared to conventional treatment. The research implies that early treatment to prevent the onset of epilepsy may help to reduce the intellectual disability in individuals with TSC, leading to positive long-term outcomes. Notably, the EPISTOP study also reports that preventive treatment proved to be effective in preventing infantile spasms [12].

Ongoing research aims to optimize mTOR inhibition called rapamycin and identify additional approaches for addressing challenges in TSC. However, animal models and clinical investigations have demonstrated that mTOR inhibitors do not treat all TSC-related symptoms equally. Due to the variety of symptoms in each case of TSC, not all therapeutic approaches benefit all patients. A personalized treatment strategy is essential [5].

To enhance epidemiological data for the future, it is recommended to establish standardized reporting criteria and methods for diagnosing and recording cases of rare diseases like TSC. Creating a national registry dedicated to TSC can help centralize data collection, fostering collaboration among healthcare institutions, research organizations, and patient advocacy groups. Promoting education initiatives for healthcare professionals, incorporating technology such as electronic health records, and ensuring accessibility to genetic testing facilities are crucial steps. Longitudinal studies, international collaboration, and involving patients in data collection efforts can provide comprehensive insights. Additionally, advocating for government support and funding for rare disease research will contribute to building a stronger foundation for epidemiological data, improving patient outcomes, and advancing scientific understanding.

Conclusion

We report a case series of 2 siblings suffering from tuberous sclerosis, a congenital disorder caused by an inactivated variant of the TSC1 or TSC2 gene. This rare disease may cause morbidity and mortality due to neurological, lung, and renal complications, including massive enlargement and hemorrhage from AML and renal failure and status epilepticus. A thorough physical examination and multi-modality imaging play an important role in diagnosing this disorder, as it exhibits various subtle features across the body. Early diagnosis can facilitate a better prognosis if the patients are given proper treatment. Most symptoms of TSC can be missed until adulthood and many patients are not treated properly so the prognosis of this disease is not good. Clinician and radiologists need to diagnose TSC properly and collaboration among clinicians to manage this rare disease is recommended. Genetic tests and family counseling must be given to manage the treatment of TSC and to prevent the progression of the disease.

Patient consent

The authors of this case series titled *"A Rare Case of Siblings with Bilateral Renal Angiomyolipoma and SEGA, Various Manifestations with Severe Complications"* state that Informed consent for the publication of this case series was obtained from the legal guardians of the pediatric patients involved. All patient identifying information has been redacted to protect the privacy of the individuals involved.

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