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Serial Glioblastoma Case in Young Age: Rare Case

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***Abstract**: Background: Glioblastoma is the most common primary brain tumour in adulthood, accounting for 70% of all malignant brain tumours in the central nervous system.Gglioblastomas occur more frequently in adulthood (median age 64 years), they can occur at any age and rarely occur in children. Glioblastoma occurs mostly in the fifth or sixth decade of life and is rare at a young age In this case are rare because glioblastoma occurs in young age.*
Objective: To find out the characteristics of glioblastoma in young age.
Patients and Methods: In this case, glioblastoma was found in men aged 17 years and 22 years, with its location in the right frontotemporal lobe and the left frontotemporoparietal lobe—diagnosis of glioblastoma based on imaging and tumour biopsy. Imaging can be done with CT Scan, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET). The most sensitive and specific examination is MRI.
Results: In this case, both biopsies were performed with conclusions on glioblastoma and a CT scan of the head, which provided an overview of masses in the right frontotemporal lobe and left frontotemporoparietal lobe. MRI was only performed in case 2, and there was a mass in the left frontotemporoparietal lobe, mesencephalon, pons, optic chiasm, proximal right-left optic nerve, covering the left internal carotid artery to the subcutaneous left frontotemporoparietal region accompanied by fluid collection with chronic bleeding components, cerebral edema with subalpine herniation. To the right ± 9mm and a downward transtentorial herniation at the mesencephalon level, right lateral ventriculomegaly. The therapies that have been given to both patients are excision, radiotherapy and chemotherapy.
Conclusion: Both patients were diagnosed with glioblastoma based on anamnesis, physical examination, supporting examination and definitive diagnosis by histopathological examination. Both cases are extremely rare because epidomological glioblastoma is common at ages 45-65 and very rare in less than 30 years of age. Glioblastoma at a young age can occur due to genetic mutations. The genetic mutation most commonly associated with glioblastoma is the Isocitrate Dehydrogenase 1 (IDH 1) mutation. IDH1 mutation occurred in 82% of cases with secondary glioblastoma. This IDH 1 mutation is often associated with younger age and better prognosis. The IDH 1 mutation must be accompanied by a mutation of TP53 for progression to the tumour. Genetic examination is important to determine the prognosis of patient with glioblastoma.

Keywords: Glioblastoma, Adolescent, Frontotemporal Lobe, Brain Tumour, Genetic Mutation

1. INTRODUCTION

Glioblastoma is a brain tumour originating from glial cells. Glioblastoma is the most common and most aggressive and primary malignant tumour in humans, involving glial cells and 52% of all functional brain tissue tumours and 20% of all intracranial tumours [1].
The incidence of glioblastoma is approximately 50 -70% of all gliomas [2,3]. The annual incidence is 2-5 per 100,000 population [3,4]. The incidence of glioblastoma appears to be twice as common in European populations than in African Americans or Asians [3]. Although glioblastomas occur more frequently in adulthood (median age 64 years), they can

occur at any age and rarely occur in children. Glioblastoma occurs mostly in the fifth or sixth decade of life and is rare at a young age. Therefore, glioblastoma that occurs at a young age is very interesting to discuss. This tumour is more common in men than in women, with a ratio of 3: 2 [4].

Based on data from the American Cancer Society, an estimated 17,000 new cases of primary malignant brain tumours were diagnosed in 2002 in the United States (9600 male patients and 7400 female sufferers). These data represent 1.3% of all cancer types diagnosed in 2002, but an estimated 13,000 deaths in 2002 were associated with primary malignant brain tumours, approximately 2% of cancer-related deaths in the United States [5].

Tumour growth will be destructive and suppressive. Brain tissue also causes changes in brain fluid and blood. At one time, when the accommodation limit has been exceeded, the intracranial pressure will increase [5,6].

In this rare case series, glioblastoma will discuss pathophysiology, clinical symptoms, neuroimaging and treatment and prognosis, which is expected to help clinicians diagnose and manage glioblastoma.

Histological analysis has shown that only 2-7% of glioblastomas are tumour-independent rather than spread far from the leading site. Despite its rapid infiltrative growth, glioblastomas tend not to invade the subarachnoid space and, as a result, rarely metastasize via cerebrospinal fluid (CSF). Haematogenous spread to extraneural tissues is extremely rare in patients who have had no prior surgical intervention, and penetration of the dura, venous sinuses, and bone is typical [11].

Glioblastoma can be classified as a primary or secondary tumour. Primary glioblastoma accounts for the majority of cases in about 60% in adults older than 50 years. These tumours are de novo tumours that are without clinical or histopathological evidence of pre-existing ones. The clinical presentation is brief, usually less than three months. Secondary glioblastoma is about 40% usually develops in younger patients (<45 years) through the malignant progression of low-grade astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). The time required for this development varies from less than one year to more than ten years, with a mean interval of 4-5 years. An increasing number of cases indicate that primary and secondary glioblastoma are other disease developments in genetics, age, and response to therapy [11].

Symptoms that arise are a combination of compression and infiltration of tissue around the tumour, vascular compression, and elevated intracranial pressure. Thus, the symptoms present are focal and general neurological deficits. Common symptoms occur due to increased intracranial pressure, such as headaches (30-50%), nausea, vomiting, vertigo, and dizziness (dizziness). Focal symptoms indicate the tumour location, for example, hemiparesis, aphasia, visual disturbances, sensory disturbances, and depending on the location, size, and speed of growth [12].

These tumours are most often located in the frontal and temporal lobes. If located in the frontal lobe, these tumours can produce behavioural changes and contralateral spastic paralysis due to compression of the precentral sulcus. Motor aphasia occurs when the tumour presses on Broca's area, and seizures are also standard in tumours in the frontal lobe. Tumours in the dominant hemisphere's medial temporal lobe can cause verbal memory impairment, and lesions in the non-dominant hemisphere can cause visuospatial memory impairment. In contrast, tumours in the anterior temporal lobe do not cause symptoms until they are large enough. Sensory aphasia can occur in posterior temporal lobe tumours [12].

Chemotherapy also plays a role in the treatment of glioblastoma. Although optimal chemotherapy regimens do not exist, several studies have shown that postoperative chemotherapy can also improve survival rates. Currently, temozolomide is used at a dose of

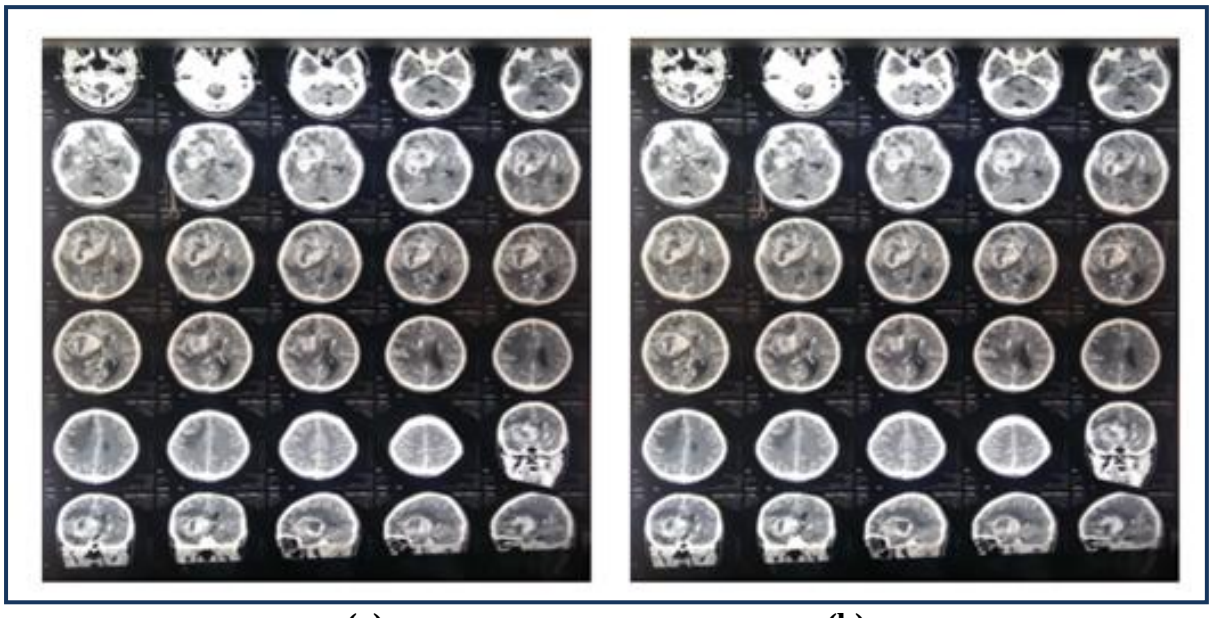
150 mg / m2 or a combination of vincristine and procarbazine. The primary mechanism of temozolomide is by damaging the DNA of tumour cells, causing tumour cell death [10,15].
Most glioblastomas will. The mean time to recurrence after treatment for newly diagnosed glioblastoma was 7 (seven) months. The clinical features of relapse are often the same at baseline in diagnosis. When the progression of the tumour is known, it requires appropriate treatment. The prognosis for glioblastoma is poor despite aggressive treatment. The mean survival rate in patients diagnosed with glioblastoma is approximately one year [10]. Patients with surgery followed by radiotherapy have a mean survival of 50 weeks [15]. The mean survival for patients with recurrence of glioblastoma is 4 (four) months. However, some patients have a relatively long survival rate (> 5 years).

2. OBJECTIVE

The objective of this study is to find out the characteristics of glioblastoma in young age.

3. CASE REPORT

The two cases were male patients aged 17 years and 22 years. The first patient's main complaint is a headache. Current medical history: The headache has worsened since two months ago, accompanied by left half body weakness. History of CT Scan of the Head with Glioblastoma Multiforme results. A history of two seizures starting on the left side of the body and then spreading throughout the body. From birth, the patient has difficulty communicating.
The second patient's chief complaint is headache. Patient also complained of being forgetful and communication increasingly difficult since the beginning of April 2018. History of being diagnosed with a brain tumour since August 2017 with the results of PA Glioblastoma Multiform Grade 4 with complaints of decreased consciousness, slumping and slumping and headache. History of symptomatic epilepsy since four months ago with OAE Phenytoin 3X100 mg and controlled.



(a) (b)

Fig 1. (a) CT Scan Results of The First Patient (b) CT Scan Results of The Second Patient

(a) CT Scan result of the first patient with Glioblastoma Multiforme. (b) CT Scan results of the second patient with Glioblastoma Multiforme. In the CT scan results the first patient showed a relatively fixed intraaxial mass of the right frontotemporal lobe, cerebri edema with subfalcine herniation to the left as far as ± 1.3cm, transcranial herniation as far as ± 1.9 cm, downward transtentorial herniation as high as mesencephalon level, leptomeningeal stinging in right temporoparietal regio suspek leptomeningeal metastases, and severe communicans hydrocephalus increase.

Besides, the CT Scan results of the second patient showed a heterogeneous intraracial solid mass with vasogenic edema around it, on the right frontotemporal lobe, accompanied by a calcified component, with a necrotic area, size ± 7.32x5.52x5.25cm, substantial after the increase in contrast (density ± 30 to ± 60HU). Leptomeningeal enhancement in the right temporoparietal region suspected leptomeningeal metastases. Hydrocephalic communication severity is increasing. Suspected bilateral mastoiditis, left maxillary sinusitis, deformity of the left ocular bulb, suggesting bulbs physics, and left basal ganglia calcification.

(a) Histopatology result of the first patient with Glioblastoma Multiforme (WHO Grade 4). (b) Hystopatology results of the second patient with Glioblastoma Multiforme (WHO grade 4).

Histopatolgy results of the first patient show as macroscopically, tissue with a diameter of approximately 1-1.5 cm (3 pieces) was received, soft, grayish-white, and processed in 1 cassette. Meanwhile, microscopically, it shows pieces of tissue containing tumours consisting of proliferating polygonal cells.

While in the histopatology results of the second patient was shown macroscopic tissue measuring 7x5x3 cm diameter 3.5-4 (3pcs) and tissue small as much as 3 cc, brownish gray color. On the slices appear a brittle part, partially dense partially blackish. Microscopicly visible pieces of tissue consist of the proliferation of cells with round-oval nucleus, pleomorphic, hyperchromatic, coarse chromatine, atopic mitosis approximately 16/10 HPF, accompanied by Bizzare cells, composed solidly accompanied by necrosis area. There is also an endothelial proliferation and bleeding area.

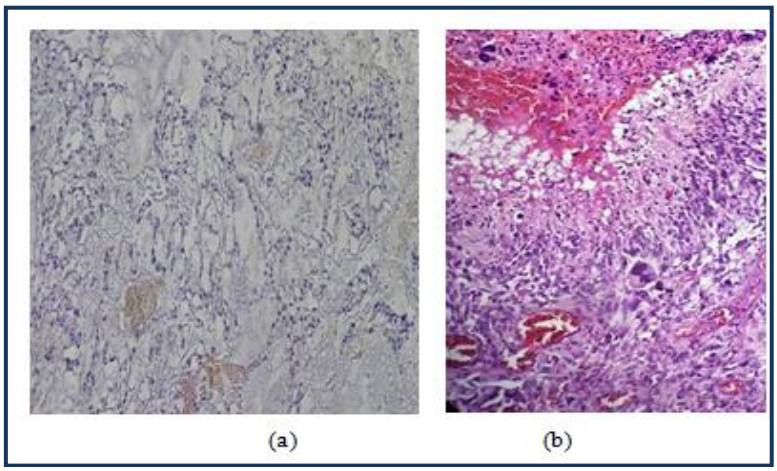


Fig 2. Histopatology Results of Glioblastoma

The result of Second patient's head CT scan without contrast shows hyperdense crescentic lesions in the left frontotemporal region with air density lesions in them, hyperdense lesions filling the sulci of the left frontotemporal region, hypodense lesions of firm boundaries on the left thalamus, narrow sylvii fissure sulci and gyrii. Flattened, differentiated white and gray matter blurred in the left cerebral hemisphere, the left lateral ventricular system is narrowed III, IV and cisternal normal, showing a left midline shift of ± 8 mm. Head CT scan of the second patient without contrast showed that enhanced multiple ring cystic essences in the left

temporal lobe were suspected of the late capsule-phase cerebral abscess, cerebral edema with subalpine herniation to the right ± 10 mm, and mild obstructive hydrocephalus as high as ventricular II level.

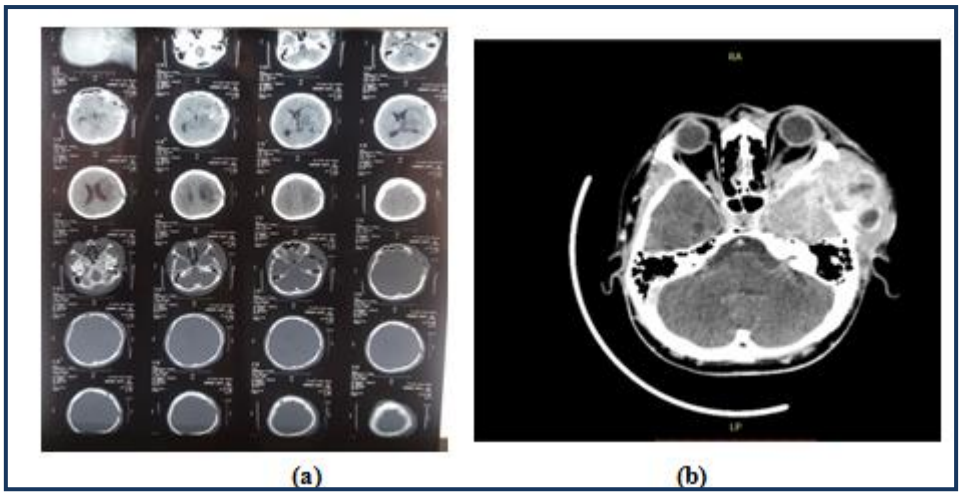


Fig 3. (a) The Second Patient's CT Scan Without Contrast Results (b) Contrastless CT Scan Results of The Second Patient

The head's MRI results without contrast showed masses in the left frontotemporoparietal lobe, mesencephalon, pons, chiasma opticum, right and left proximal optic nerve, covering the left internal carotid to the subcutaneous left frontotemporoparietal region accompanied by fluid collection with a chronic bleeding component. Cerebral edema with subalpine herniation to the right ± 9mm and a downward transtentorial herniation at the mesencephalon level. Right lateral ventriculomegaly.

CRX results show that the size of the normal position, the aorta does not appear to be elongated, dilated, or calcified. Normal vascular markings, normal hilum D / S, and no visible infiltrate / cavity/nodule. Intake visible bone, no visible lesion lytic / blastic / line / fracture. The therapies that have been given to both patients are excision, radiotherapy, and chemotherapy.

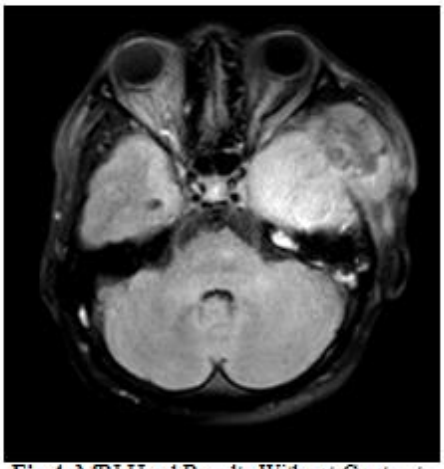


Fig 4. MRI Head Results Without Contrast Of Second Patient

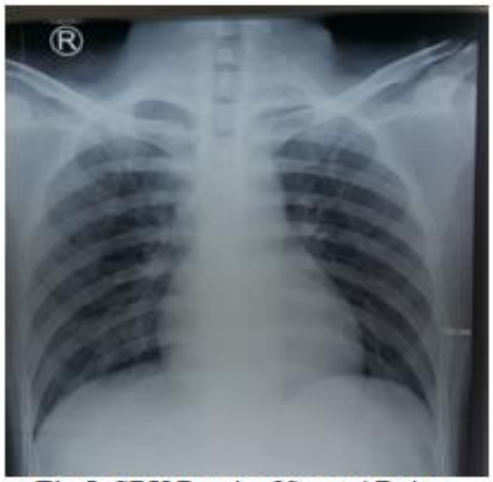


Fig 5. CRX Result of Second Patient

Figure 3. (a) The Second Patient's CT Scan Without Contrast Results (b) Contrastless CT Scan Results of The Second Patient

4. DISCUSSION

In both cases, the patients were very young, namely 17 years and 22 years of the same sex, namely men. Epidemiologically, glioblastoma is a brain tumour that develops from erythrocytes. Glioblastoma is a primary tumour of the central nervous system that is the most malignant and occurs most often in adults, which is about 33 - 45% of all primary brain tumours. Glioblastoma occurs more frequently in men than women (3: 2) and usually occurs in patients over 50 years of age, with a peak incidence of 65-74 years [10,15].

Glioblastoma at a young age can occur due to genetic mutations. The genetic mutation most commonly associated with glioblastoma is the Isocitrate Dehydrogenase 1 (IDH 1) mutation, which occurs in about 10-12% of glioblastoma cases. IDH1 mutation occurred in 82% of cases with secondary glioblastoma [16]. This IDH 1 mutation is often associated with younger age and better prognosis [17]. The IDH 1 mutation must be accompanied by a mutation of TP53 for progression to the tumour. Secondary glioblastoma develops from a low-grade tumour and usually occurs at a young age.10 In secondary glioblastoma, the most frequent mutations are IDH1 and TP53 [16,18].

Peter Black argues that the nature of headaches such as waking up the patient at night (10-32%) or getting more massive on waking up and getting better as the day progresses (15-36%), the headache gets worse when the patient changes position, coughing, or exercising (20-32%), new headaches that differ from the usual or more severe headaches, with nausea or vomiting (30-40%), papilledema or focal neurological signs. Patients with chronic progressive headaches with seizures, changes in behaviour and neurological disorders need to undergo a further assessment with CT-scan or MRI.

The complaints felt in both patients, in this case, were the same. Namely, both complained of worsening headaches, weakness in half body, seizures, tend to be drowsy and a behaviour change. The neurological examination in these two patients on motor examination obtained lateralization. What distinguishes these two patients is that in the second patient, a positive regression reflex is obtained.

Clinical signs and symptoms in glioblastoma are divided into two non-specific signs of increased intracranial pressure and specific tumour location signs. The non-specific signs consist of headache, drowsiness, visual disturbances, nausea, vomiting, neck stiffness, papilledema, and sometimes abducent nerve palsy. Specific signs due to the tumour's variable location include motor, sensory, vision, language, and speech disturbances. On the CT scan of the head with contrast in these two patients, it was found that there was an interracial mass in the right frontotemporal lobe, cerebral edema and herniation in the first patient. Meanwhile, the second patient showed a hypodense lesion with a clear border of the left thalamus, hyperdense lesions on the left frontotemporal, cerebral edema and hernia. The CT scan images in these two patients supported a tumour image, namely glioblastoma.

MRI examination was only performed in the second patient with a mass in the left frontotemporoparietal lobe, mesencephalon, pons, chiasma opticum, proximal optic nerve, right and left, cerebral edema with herniation and right lateral ventriculomegaly. Histopathological examination was performed on these two patients. Histopathological examination is critical to support diagnosis and determine the type of tumour. The histopathology of these two patients showed a Glioblastoma.

The diagnosis of glioblastoma can be confirmed by imaging and biopsy of the tumour. On biopsy, glioblastoma can be characterized by necrosis or cell death that is not present in astrocytoma anaplasia [20]. Microscopically, glioblastoma shows nuclear pleomorphism, mitotic activity, endothelial hyperplasia, and necrosis. Three of the four microscopic characteristics are biased to diagnose glioblastoma.

In these two cases, the history, physical examination and the results of supporting examinations support a cerebral tumour, which is a glioblastoma based on WHO 2016 criteria. For a morphological diagnosis based on WHO, if viewed based on age, both cases include IDH-mutant, but if seen from the tumour's progression into the IDH-wildtype. Other therapeutic modalities given in both cases were tumour resection, radiotherapy and chemotherapy. The management of patients with glioblastoma to date has not been satisfactory. The management of standard glioblastoma includes general management and specific management. General treatment includes managing symptoms such as headache (TTIK sign), seizures, hemiparesis, cognitive deficits, speech deficits and other symptoms. Specific treatment includes surgery, followed by radiotherapy and chemotherapy. If the tumour cannot be operated on, then radiation therapy and chemotherapy can be used [19]. Surgery plays a crucial role in the management of glioblastoma patients. Indications include confirming the histopathological diagnosis, reducing the tumour, eliminating the mass's effects, and performing cerebrospinal fluid (CSF) diversion measures. Relative contraindications include a weak medical condition, a worsening condition, and difficulty reaching the tumour's location. Surgical options consist of stereotactic biopsy, open biopsy, debulking and total resection. Several studies have shown that total resection is associated with improved prognosis.

They received the same therapy in both cases, namely tumour resection, then concomitant radiotherapy and temozolomide. Management in both cases was following the theory and guidelines for the management of glioblastoma. In the second case, there was a very rapid recurrence rate of about two months post-resection. It can be seen from the CT scan results in August (post-resection) compared to the CT scan in November (post-radiotherapy). The rapid recurrence in these patients could be due to several factors because the radiotherapy dose may not be optimal and may be resistant to temozolomide.

In the first case, the patient died within two months of diagnosis and received 12X radiotherapy and chemotherapy with 14 days of temozolomide (1x100 mg). Whereas in the second case, the patient still survived from diagnosis to completion of therapy consisting of resection, radiotherapy (3X13 Gy) and chemotherapy for 23 days with temozolomide (1X100 mg). The progression/recurrence of tumour cells was very fast. Patients' survival rate in these two cases is likely to be significantly influenced by poor PPR before undergoing therapy, which is 50%, even though both are young.

5. CONCLUSION

In this case, glioblastoma was found in males aged 17 years and 22 years, with its location in the right frontotemporal lobe and the left frontotemporoparietal lobe. In this case, both biopsies were performed with conclusions on glioblastoma and a CT scan of the head, which provided an overview of masses in the right frontotemporal lobe and left frontotemporoparietal lobe. Based on these two cases, it may provide input that early detection and examination of molecular markers of brain tumours are vital. The therapies that have been given to both patients are excision, radiotherapy, and chemotherapy. Genetic examination is important to determine the prognosis of patient with glioblastoma.

Abbreviations

CT: Computerized tomography; MRI: Magnetic resonance imaging; Positron Emission Tomography (PET)

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Yulia Damayanti and Dessika Rahmawati
the clinical part of the study, analysed the data and wrote with meticulous
revision the paper. All authors read and approved.

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Availability of data and materials
The data supporting our findings can be found with the corresponding
author and can be contacted through the following e-mail: y.damay83@gmail.com

Consent for publication
Available, it was obtained from patients and parentsof the studied group.

Competing interests
The authors declare that they have no conflict of interest.

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