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CASE REPORT **OPEN ACCESS**

EPILEPSY AS THE MAIN CLINICAL MANIFESTATION OF CONGENITAL HYPOTHYROIDISM: A RARE CASE REPORT

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ABSTRACT

Background: Congenital hypothyroidism (CH) is defined as a deficiency of thyroid hormones present at birth and is one of the most common causes of intellectual disability. CH shows several manifestations, but it is rarely reported that CH manifests as epilepsy. To our knowledge, this rare manifestation of congenital hypothyroidism has only been reported four times previously. The potential association between CH and epilepsy remains unclear.
Case: We reported a rare case of a 1-year-old child who presented to the emergency department with complaints of recurrent seizures. Laboratory results showed increased TSH levels and decreased FT4 levels. Electroencephalography (EEG) results were expected. The patient was diagnosed with epilepsy and congenital hypothyroidism. The patient received stabilization therapy in the ER and was admitted to the PICU for 7 days. During hospitalization and a seven-day evaluation at home, the patient did not experience any further seizures.
Discussion: Epilepsy and congenital hypothyroidism can affect each other through three known pathogeneses: mitochondrial dysfunction, oxidative stress, and failure of amino acid regulation in the brain. Long-term use of some anti-epileptic drugs is known to reduce thyroid hormone levels.
Conclusion: Thyroid hormones play an essential role in various aspects of epilepsy. Thyroid function screening in patients with epilepsy may be advisable, especially in patients with developmental disorders and relevant symptoms.

Keywords: congenital hypothyroidism, epilepsy, pathogenesis, seizure

Introduction

Thyroid hormone is a hormone produced by the thyroid gland that synthesizes thyroxine (T4) and triiodothyronine (T3) hormones.[1] The thyroid hormone plays a vital role in cell metabolism and nerve development. More specifically, the thyroid hormone works on neuron differentiation, synapse development, and myelination in the prenatal and newborn periods.[2] Thyroid hormones also play a role in the early formation of cells, mitochondrial biogenesis, and neuroprotection in brain cells.[3]

Thyroid hormone deficiency that occurs since birth is defined as congenital hypothyroidism (CH). It is one of the most common causes of intellectual disability. The incidence ranges from 1:3,000 to 1:4,000 live births worldwide.[2] In Indonesia, this ratio is higher, specifically 1:2513, from 14 provinces that have been studied.[4] Based on medical record data at Dr. Cipto Mangunkusumo Hospital and Hasan Sadikin Hospital, only 2.3% of CH cases were diagnosed at an age of less

than three months, and most CH cases (>70%) were diagnosed at an age over one year with permanent mental deficit conditions.[5]

Among the manifestations of CH are oversleeping, feeding problems, lethargy, constipation, hoarse crying, and on physical examination, there are macroglossia, wide fontanelle, umbilical hernia, prolonged jaundice, spots on the skin, and dry skin. However, these manifestations usually only appear a few months or years after birth; only 5-10% of newborns show symptoms at birth.[5]

CH rarely manifests as epilepsy. Epilepsy is a disorder of recurrent and spontaneous seizures that can cause permanent changes in the normal function and morphology of nerve cells and even cell death. Several factors that modulate the pathogenesis of epilepsy have been identified, including mitochondrial dysfunction, oxidative stress, and failure in the regulation of excitatory (glutamate) and inhibitory (GABA) amino acids in the brain.[6] Based on the known influence of thyroid function on these factors, thyroid deficiency has been associated with epileptic seizures.

In this case report, we report a 1-year-old child who had recurrent seizures and a history of CH and epilepsy. To our knowledge, this rare manifestation of congenital hypothyroidism has only been reported four times previously.[7–11] This phenomenon is rarely reported and requires in-depth research regarding its pathogenesis.

Case Report

A 1-year-old child presented to the emergency department with complaints of recurrent seizures. The seizures lasted for 7 minutes and occurred 4 times. The seizures involved the whole body, and the patient was unconscious during the episodes. Upon arrival in the emergency department, the patient had another seizure lasting 10 minutes.

The first seizure occurred when the patient was 2.5 months old. The mother's pregnancy history showed no significant diseases or medication use. The patient was born spontaneously via vaginal delivery at 32 – 33 weeks gestation due to premature rupture of membranes. The amniotic fluid was cloudy, and the baby did not cry immediately after birth. The patient was admitted to the PICU for 3 days due to respiratory distress.

On physical examination upon arrival, the patient was lethargic and exhibited coarse facial features. Vital signs included a heart rate of 100 beats per minute, respiratory rate of 24 breaths per minute, axillary temperature of 36.6°C, and oxygen saturation of 100% with a nasal cannula at 2 liters per minute. Her body weight was 9 kg. On general status examination, the patient was conscious, with a Glasgow Coma Scale (GCS) score of 15. Neurological examination revealed diminished biceps reflexes on both sides. There was a developmental delay, including hypotonia, as the patient was still unable to grasp objects.

A comprehensive blood test was regular. The result of electrolyte serum shows a non-significant decrease in potassium at 3.46 mmol/L and a non-significant increase in chloride at 118.62 mmol/L. Further laboratory results showed a TSH level of 32.17 µU/mL (9 – 20 µU/mL) and an FT4 level of 0.12 pmol/L (0.25 – 5.0 pmol/L). Electroencephalography (EEG) results were expected (Figure 1). The patient was then diagnosed with status epilepticus, epilepsy, and congenital hypothyroidism.

In the ER, the patient was given an intravenous infusion of D5 ½ NS 800 mL/day, intravenous phenytoin 180 mg in 20 mL NaCl 0.9% at a 40 mL/hour rate for 30 minutes. After 12 hours, she received two doses of intravenous phenytoin 25 mg each, paracetamol 100 mg orally thrice daily if fever occurs, and oral valproic acid 2.5 mL twice daily. Valproic acid's primary functions are related to modulating neurotransmitter activity and stabilizing electrical activity in the brain**,** and oral L-thyroxine 50 mg once a day is its synthetic form of the thyroid hormone T4 (thyroxine). The patient was admitted to the PICU for 7 days. The next day during hospitalization, the patient experienced a seizure 2 times a day, with a duration of each seizure of 10 minutes. The vital signs were normal, including heart rate, respiratory rate, axillary temperature, and oxygen saturation. On the third and fourth day, the patient had another seizure, but the frequency decreased; she experienced a seizure 1 time a day, with a duration of 3 minutes. The vital signs were stable.

From the fifth day until the last day of hospitalization, the patient did not experience any more seizures. The patient was conscious, and the vital signs were normal. The patient was then discharged on the seventh day of hospitalization and given home medication in the form of oral valproic acid 2.5 mL twice a day, and L-thyroxine 50 mg once a day. Then, the pediatrician scheduled an evaluation once a week after the patient was discharged for clinical evaluation and therapy. After one week of thorough evaluation, it was observed that the patient did not experience any seizures while staying at home. The patient's vital signs remained stable throughout this period, and there was a noticeable improvement in activity levels, with the patient becoming more active and responsive. Considering these positive developments, the pediatrician continued the previously prescribed therapy without any modifications. The pediatrician also advised the patient and their family to return for a follow-up check-up if any symptoms or complaints arise in the future.

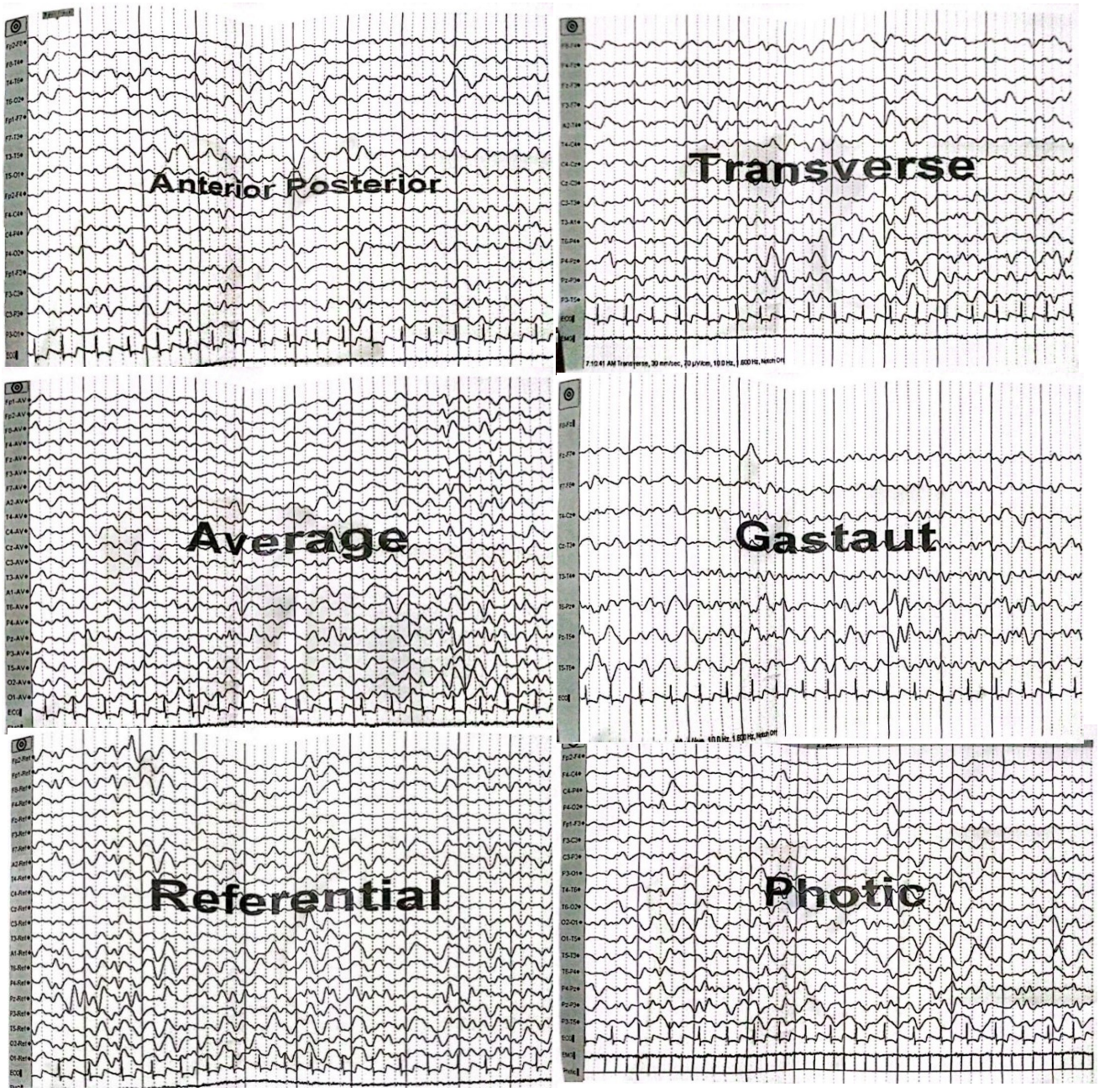

Figure 1. Electroencephalography (EEG) showing there is no abnormalities

Discussion

Epilepsy is defined as a group of typical seizure types and electroencephalography (EEG) images that are often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious). The highest incidence of epilepsy is in individuals with an age range of 0-5 years and over 65 years.[7] However, congenital hypothyroidism is rarely associated with seizures in babies. The case in this article shows that epilepsy is the primary clinical manifestation of congenital hypothyroidism. The patient was born at 32-33 weeks' gestational age due to premature rupture of the membranes and cloudy amniotic fluid, as well as respiratory distress at birth. At the age of 2.5 months, the patient had her first seizure and has been consuming anticonvulsants for four months. Since the first seizure, the patient has had recurrent seizures, requiring hospitalization. Investigations have been carried out to rule out other causes of seizures, such as EEG and laboratory features that show expected results. Based on the symptoms and clinical signs, the patient was examined for thyroid function. The results showed high TSH levels and low FT4. The patient was diagnosed with congenital hypothyroidism with epilepsy.

Several similar cases have been reported. Based on our investigation, four cases have been previously reported.[7,8,10,11] Some of them manifest as epilepsy and CH alone, but some also have other manifestations. Sproul et al. reported a patient with CH and epilepsy. The patient's mother had a history of mild hypothyroidism and was taking thyroxine during pregnancy.[8] Another case reported by Aly et al reported a patient with CH accompanied by epilepsy. The patient was born by cesarean section and had respiratory distress at birth. The patient's mother was also undergoing treatment for hypothyroidism, gestational diabetes, and antidepressant therapy during pregnancy.[10] The third case was reported by Sutsko et al. In that report, the patient's mother had a history of autoimmune hypothyroidism and was not taking regular medication. At birth, the patient had respiratory distress and sepsis.[11] The following case was an 8-year-old boy who suffered from CH and epilepsy, also accompanied by short stature and malnutrition. The patient was also taking recombinant human growth hormone (rhGH). During the use of the drug for 6 months, the patient had three seizures. Then the use of rhGH was suspended, and the anticonvulsant drug levetiracetam was given. The seizures were controlled again, and the relationship between rhGH and thyroid dysfunction and seizures is still unclear. Several factors that modulate the pathogenesis of epilepsy, including mitochondrial dysfunction, oxidative stress, and failure of the regulation of excitatory (glutamate) and inhibitory (GABA) amino acids in the brain, are thought to be strongly influenced by thyroid hormones. Other sources state that hypothyroidism can trigger severe hyponatremia, which can cause seizures.[13]

Thyroid hormones (TH), primarily T3, regulate mitochondrial function and biogenesis through three main mechanisms: direct binding to mitochondrial receptors (P43), interactions with thyroid hormone receptors (TR) to regulate proteins encoded by the nucleus, and activation of intermediating factors such as PPARγ, NRF-1, and PGC-1α. These mechanisms affect the expression of mitochondrial genes and promote biogenesis. TH also plays a key role in energy metabolism by increasing oxygen consumption and ATP hydrolysis, mainly through increased proton leakage along the mitochondrial membrane. This proton leakage is facilitated by changes in membrane fluidity and barker protein expression (UCP), which disrupt oxidative phosphorylation from ATP synthesis.[6]

Decreased TH activity is associated with decreased mitochondrial function, while TH treatment can restore mitochondrial function, especially in cells with mitochondrial DNA deficiency. TH significantly affects brain structures such as the striatum and cerebral cortex, modulating mitochondrial genes and oxidative phosphorylation capacity. Hypothyroidism during brain development is associated with impaired mitochondrial function, but specific receptors and mechanisms through which TH can affect mitochondria during development are still unclear.[6]

Dysregulation of thyroid hormones, both hypothyroid and hyperthyroid, affects the balance of antioxidants and oxidants, thereby increasing the formation of Reactive Oxygen Species (ROS) and the formation of oxidative stress that plays a vital role in the seizure mechanism in epilepsy. In addition, mitochondrial dysfunction can directly increase ROS production. Conversely, excessive ROS levels also increase mitochondrial damage. This causes a vicious cycle in which they damage each other.[14] Oxidative stress is involved in a variety of acute conditions, such as cerebral ischemia, and chronic neurological conditions, including epilepsy.

Mitochondrial dysfunction is involved in about 60% of all acquired epilepsy. As a result of mitochondrial dysfunction, ROS production increases, and cytosolic Ca2+ concentrations increase. This leads to overstimulation, increasing ATP consumption, and energy depletion. This results in necrotic or delayed apoptotic cell damage and death. This neuronal cell death increases glutamate release and hyperexcitability, leading to recurrent seizures.[15-16]

According to several studies that have been conducted, it is proven that GABA neurons modulate the functioning of the thyroid system. Generally, GABA will inhibit thyroid function in the hypothalamus, pituitary system, and thyroid (Figure 2). In addition to this bidirectional interaction between GABA and thyroid hormones, GABA also plays a vital role in seizure suppression, i.e., as an inhibitory neurotransmitter. Thus, it can be assumed that thyroid hormones can inhibit seizures by increasing the GABAergic system and brain development.[6]

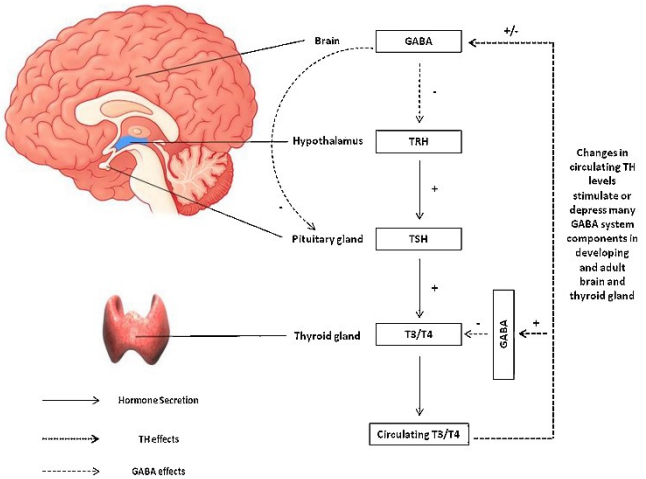

Figure 2. Schematic interaction between the thyroid system and GABA in vertebrates. The + and − symbols indicate stimulation and inhibition, respectively. GABA, γ -γ-aminobutyric acid; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine[6]

In several studies, Long-term use of anti-epileptic drugs (AEDs) can reduce thyroid function. Some of them are carbamazepine, phenobarbital, phenytoin, valproate, and oxcarbazepine. Some antiepileptic drugs that do not affect thyroid levels include lamotrigine, levetiracetam, topiramate, tiagabine, and vigabatrin.[6,17–20] In patients with CH who have seizures, it is necessary to choose the right AED so as not to worsen the hypothyroid condition.

Conclusion

Thyroid hormones significantly influence brain development and function. Congenital hypothyroidism, although rarely presenting as epilepsy, should be considered in the differential diagnosis when young children present with seizures. Prompt diagnosis and treatment with hormone replacement can mitigate neurological consequences.

In addition, Physicians also need to screen thyroid function in pediatric patients with epilepsy, especially if accompanied by developmental disorders or symptoms and clinical signs that indicate thyroid dysfunction. Physicians should be cautious in the use of antiepileptic drugs in epileptic patients with CH, as some AEDs may decrease thyroid levels.

Limitations

This study has several limitations. This study shows a case report of one patient. Thus, the long-term prevalence of epilepsy in CH in individuals is not observed. The next weakness is that our results do not prove that CH may improve epilepsy outcomes, so further studies are needed to determine how CH may impact clinical practice.

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