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Phenytoin Induced Transient Chorea in a 9-Month-Old Baby Boy with Japanese Encephalitis

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Abstract: ***Background: Phenytoin is a common anticonvulsant drugs used in children for treating acute seizures and status epilepticus. Chorea is a rare side effect of anticonvulsant. It has been proposed that phenytoin may cause chorea through enchancement of the central dopaminergic pathway in the basal ganglia.Case: A 9-month-old male patient weighing 7.8 kg was admitted to the emergency room in S Hospital with loss of consciousness and seizure. Patient was diagnosed as viral encephalitis, admitted to PICU and treated with anticonvulsant according to guidelines of acute seizure. Phenytoin loading dose of 20 mg/kg/dose was continued with maintenance dose of 5mg/kg/day to control seizures. On the 6th day of therapy, patient developed involuntary, continuous, uncontrolled jerky movement of head, upper limbs and lower limbs. Those involuntary movements typically were referred to chorea. The patient did not fullfill the Jones criteria for acute rheumatic fever, so he was suspected of suffering from drug-induced chorea with phenytoin being an offending agent. Phenytoin was withdrawn then oral valproic acid (15 mg/kg/day) and intravenous diphenhidramine (1 mg/kg single dose) were added. The serum phenytoin level was within normal limits (14 ug/mL). The CSF IgM antibody of Japanese Encephalitis Virus (JEV) was positive. The Naranjo's scale was 5 that showed the relationship between phenytoin and chorea was probable. The chorea had improved and disappeared completely within 5 days after phenytoin stopped. Conclusion: Chorea may occur as the side effect of phenytoin therapy. Chorea improved and disappeared after the withdrawal of phenytoin. Phenytoin induced chorea should be considered as one of the causes in patients who develop choreiform movements and on phenytoin therapy.***

Keywords: phenytoin, chorea, side effects, children

1. Introduction

Phenytoin is a common anticonvulsant drugs used in children for treating acute seizures and status epilepticus. Phenytoin is a hydantoin derivative and a non-sedative antiepileptic agent with anticonvulsant activity [1],[2]. Phenytoin exerts its anticonvulsant effect primarily by an action on voltage-dependent Na^+ channels. Phenytoin promoting sodium efflux from neurons located in the motor cortex reducing post-tetanic potentiation at synapses [2],[3].

The use of phenytoin may cause some side effects that are mostly associated with chronic use and high doses, including gingival hyperplasia, ataxia, nausea, nystagmus and tremor [4]. Chorea is a rare side effect of phenytoin. Several case reports have described phenytoin induced chorea [5]-[11]. Some case reports indicate that phenytoin induced chorea is commonly been observed in children, although it may also occur in adults [8].

Chorea refers a movement disorder marked by irregular, abrupt, non-stereotyped, random, involuntary movements. Although not completely understood, current evidence suggests that chorea results from the imbalance in the direct and indirect pathways in the basal ganglia circuitry. The disruption of the indirect pathway causes a loss of inhibition on the pallidum, allowing hyperkinetic movements to occur [12],[13]. In addition, enhanced activity of dopaminergic receptors and excessive dopaminergic activity are proposed mechanisms for the development of chorea at the level of the striatum [12].

Although rare, this side effect associated with the use of phenytoin is an important differential diagnosis among involuntary movement disorders and need to be characterized further. We report a-9 month old baby who develop transient chorea that may occur as the side effect of phenytoin therapy.

2. Case

A 9-month-old male patient weighing 7.8 kg was admitted to the emergency room (ER) in S General Hospital with loss of consciousness and convulsion. The loss of conciousness occurred 1 hour before admission. His parents said that he looked blank and sleepy. Two hours before admission, patient had generalized tonic clonic seizure that lasted for 10 minutes and stopped spontaneously. The seizure accompanied with fever. Patient complained of fever 4 days before admitted with range temperature 38.0-38.6^{o}C. Patient did not have cough, cold, shortness of breath and diarrhea. There was no history of seizure. He had no other medical problems and his family history was negative for seizure or abnormal movements. The growth and development prior seizure was within normal limits. History of immunization was completed accordance to Ministry of Health recommendation. History of JE immunization was denied. Patient lives in Karangasem, Bali Province in rural and agriculture area. There is a pig pen located 50 meters from patient's house.

On physical examination in emergency room, patient was unconscious (GCS was 7). His blood pressure, pulse and respiratory rate was within normal limits. Patient was normocephaly, no bulging of fontanelle. Sclera was not

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icteric, conjunctiva was not pale, pupil isocor with good light reflex. The ear, nose, and throat examinations were in normal limit. There was no lymph nodes enlargement found on the neck. The chest was symmetrical both on rest and movement, breath sound was bronchovesicular without rales or wheezing, the first and second heart sound were normal, regular and no murmur in auscultation. The abdomen was not distended, no hepatosplenomegaly. On neurological examination, there was no meningeal sign found in this patient. The power and tone of the superior and inferior extremities were normal. Bilateral Babinsky's sign was positive.

Laboratory findings showed hemoglobin 9.7 g/dL, hematocrit 29.2%, leucocytes $3.4x10^3$/uL, platelet $110x10^3$/µL, normal serum electrolyte and blood sugar. Cerebrospinal fluid (CSF) showed clear fluid, 3 cells/uL, 100% mononuclear cells, Nonne and Pandy reaction was negative, protein 0.02 g/dl and glucose 49 m/dl. The Japanese Encephalitis Virus-specific IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) test in CSF and serum was obtained. The head CT-scan when admitted to ER was normal. Patient was diagnosed as viral encephalitis, admitted to PICU and treated with anticonvulsant according to guidelines of acute seizure. Phenytoin loading dose of 20 mg/kg/dose was continued with maintenance dose of 5mg/kg/day and dexamethasone 1 mg/kg/day were given to control seizures and encephalitis. After therapy, patient consciousness gradually improved and he was alert in 4^{th} day of therapy.

On the 6^{th} day of therapy, patient developed involuntary, continuous, uncontrolled jerky movement of head, upper limbs and lower limbs. Those involuntary movement typically was referred to chorea. The chorea got worse when patient agitated and not appeared when he asleep. Other complaints such as fever, seizures, nausea, vomiting and diarrhea was denied. On the physical examination, patient was alert, his vital sign was within normal limits, no sign of dehydration, other general examination was within normal limits. On neurological examination, there was no meningeal sign found in this patient. The power and tone of the superior and inferior extremities were normal, the physiological reflex was normal, no pathological reflex was found. The evaluation of complete blood count, serum electrolyte and blood sugar were within normal limit. The serum phenytoin level was 14 µg/mL (reference range: 10-20 µg/mL). After chorea developed, we evaluated the head CT scan and revealed no sign of structural damages of basal ganglia or other brain impairment. The CSF IgM antibody of Japanese Encephalitis Virus (JEV) was revealed positive in 6^{th} day of admission. The patient did not fullfill the Jones criteria for acute rheumatic fever, so he was suspected of suffering from drug-induced chorea with phenytoin being an offending agent. The Naranjo's scale was 5 that showed the relationship between phenytoin and chorea was probable. Phenytoin was withdrawn then oral valproic acid (15 mg/kg/day) and intravenous diphenhidramine (1 mg/kg single dose) were added. The chorea had improved and disappeared completely within 5 days after phenytoin stopped.

3. Discussion

Japanese encephalitis is one of main causes of viral encephalitis worldwide and considered as one of community health problems in Southeast Asia and Western Pasific country including Indonesia. Japanese encephalitis is vector-borne zoonotic viral disease caused by Japanese Encephalitis virus (JEV) [14],[15]. The incidence of JE in endemic countries reaches 5.4/100,000 children in the age group 0-14 years and only 0.6/100,000 cases in the age group over 15 years. Eighty-nine percent of JE cases are found in children younger than 15 years of age [16]-[18]. Japanese encephalitis mortality varies by 30-70% and some cases resulting severe sequalae including paralysis and mental retardation [17],[18]. Bali is the province with the highest incidence of JE in Indonesia. Data from surveillance JE in 2015 showed there was 22 cases of JE in Bali Province of total 40 JE cases in Indonesia [19]. Japanese encephalitis virus is transmitted to human through the bite of infected *Culex* species mosquitoes. The virus is maintained in a cycle between mosquitoes and vertabrate hosts, primarily pigs and wading birds. Japanese encephalitis virus transmission occurs primarily in rural agricultural areas, often associated with rice production and flooding irrigation [14],[16]. **In this case,** patient 9 month old baby boy living in Karangasem, Bali which is included in JE endemic areas in Indonesia. Patient lives in agriculture area and there is a pig pen located 50 meters from patient's house.

Most JEV infections in humans are asymptomatic. Less than 1% of people infected with JEV develop symptomatic disease. Symptomatic JEV infection can present as a nonspecific symptoms like fever, headache, and nausea which may last for several days. Patient may developed altered mental status, seizures and other neurologic symptoms that may develop over the next few days. Japanese encephalitis is diagnosed by tests detecting JE virus-specific antibodies in serum and/or cerebrospinal fluid [14]-[16]. **In this case,** patient presented with fever, altered mental status and seizures that confirmed by MAC-ELISA tests that showed positive IgM in his cerebrospinal fluid.

Seizing control is one of the main therapies in the management of encephalities [20]. Phenytoin is a common anticonvulsant drugs used in children for treating acute seizures and status epilepticus. Phenytoin is a hydantoin derivative that was first made in 1908 by German chemist Heinrich Biltz and found useful for seizures in 1936 [21]. Common side effects mostly associated with chronic use and high doses, including gingival hyperplasia, nausea, rash, drowsiness, nystagmus and tremor [4]. The occurrence of drug-induced chorea is rarely reported. Involuntary movement have been reported in patients using antiepileptic drugs, including carbamazepine, phenobarbital and phenytoin. Anticonvulsant induced chorea first reported in 1962 with phenytoin as offending agents [7],[8]. Phenytoin is primarily metabolized to its inactive form by the enzyme CYP2C9. Variations within the CYP2C9 gene that result in decreased enzymatic activity have been associated with

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increased phenytoin concentrations, as well as report of drug toxicities due to these increases concentrations [5].

The relationship of phenytoin drug levels and the induction of chorea is unclear but over half of the patients reported had levels in the toxic range (> 21mg/L) [7],[8]. The association of the administration of phenytoin with the emerge of chorea has been generally established by the timing of the movement disorder in reference to the introduction of phenytoin, the increased dosage of phenytoin, and the withdrawal of phenytoin followed by rechallange. **In this case,** patient's phenytoin plasma concentration was 14 ug/ml and did not exceed its reference range. Patient also did not present with impaired liver and kidney function that could increase the potency of the drug.

The pathophysiology of the phenytoin-induced dyskinesia has not been completely established. It has been postulated that phenytoin may cause chorea through enhancement of the central dopaminergic pathway in the basal ganglia [7]. Harrison et al. hypothesized that there is a disturbance in the functional equilibrium of the basal ganglia output systems, perhaps due to a differential effect of phenytoin on dopamine receptor subtypes or their associated second messenger system [11]. Other theory suspected the association of phenytoin and other medications may increase the risk of developing chorea [5]-[7]. Previous reported case by Barvaliya et al suggesting an interaction between phenytoin, phenobarbital and clobazam [6]. This findings is supported by other studies showing that anticonvulsant polypharmacy is associated with the occurance of chorea and only 32% patients receiving phenytoin alone [11]. **In this case,** temporal relationship between the phenytoin administration, the development of chorea, and the resolution of these movements after drug discontinuation suggest that they may have been induced by phenytoin. There was no polypharmacy of anticonvulsant in this patient. Normal head CT-scan before and after emergence of reaction has ruled out any structural damage to basal ganglia that could provoke the chorea movements.

Temporal relationship between the phenytoin administration, the development of chorea, and the resolution of these movements after drug discontinuation suggest that they may have been induced by phenytoin. An objective parameter is required to determine the causal relationship between the drug and its side effect. Naranjo's scale is a questionnaire design by Naranjo et al in 1981 for determining the likelihood of whether an adverse drug reaction is actually due to the drug rather than the results of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful [23],[24]. **In this case,** the Naranjo's scale was 5 that showed the relationship between phenytoin and chorea was probable.

The management of phenytoin induced chorea remains controversial. There is no specific treatment for this condition. In most cases, it disappeared gradually after discontinuation of phenytoin. Duration of chorea has been variable and may last hours, days or weeks after phenytoin withdrawal. In most cases, other anticonvulsant should be added to maintain the seizures by different mechanisms of phenytoin [5]-[11]. **In this case,** chorea had improved and disappeared completely within 5 days after phenytoin stopped. We added oral valproic acid (15 mg/kg/day) to maintain the seizure.

4. Conclusion

Chorea may occur as the side effect of phenytoin therapy. Chorea improved and disappeared after the withdrawal of phenytoin. Phenytoin induced chorea should be considered as one of the causes in patients who develop choreiform movements and on phenytoin therapy.

References

[1] Gallop K. Review article: Phenytoin use and efficacy in the ED. Emerg Med Australas. 2010;22:108-18.
[2] Schacter SC. Review of the mechanism of action of antiepileptic drugs. CNS Drugs. 1995;4:469-77.
[3] Delorenzo RJ, Sun DA. Phenytoin and other hydantoins mechanism of action. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 551-9.
[4] Appleton RE, Gill A. Adverse events associated with intravenous phenytoin in children: a prospective study. Seizure. 2003;12:369-72.
[5] Otarula KA, Ugarnes G, Rossi M, Balessteros D, Giano C. Phenytoin-induced chorea: Drug interaction or genetic predisposition?. Clin Neuropharmacol. 2016;39:120.
[6] Barvaliya M, Sanmukhani J, Patel TK, Tripathi CB. Phenytoin induced chorea in a pediatric patient: An interaction between phenytoin, phenobarbital and clobazam. Indian J Pharmacol. 2011;43:731-2.
[7] Zaatreh M, Tennison M, Cruz O, Beach RL. Anticonvulsants-induced chorea: a role for pharmacodynamic drug interaction?. Seizure. 2001;10:596-9.
[8] Montenegro MA, Scotoni AE, Cendes F. Dyskinesia induced by phenytoin. Arq Neuropsiquiatr. 1999;57:356-60.
[9] Filloux F, Thompson JA. Transient chorea induced by phenytoin. J Pediatr. 1987;110:639-41.
[10] Gill D, Lyons M, Allam F. Phenytoin induced chorea: a case report. Am J Ther. 2017:1;2765.
[11] Harrison MB, Lyons GR, Landow ER. Phenytoin and dyskinesias: a report of two cases and review of the literature. Mov Disord. 1993;8:19-27.
[12] Bhidayasiri R, Truong DD. Chorea and related disorders. Postgrad Med J. 2004;80:527-34.
[13] Walker RH. Differential diagnosis of chorea. Curr Neurol Neurosci Rep. 2011;11:385-95.
[14] Solomon T, Dung NM, Kneen R, Gainsborough, Vaughn DW, Khanh VT. Japanese Encephalitis. 2000;68:405-15.
[15] Batchelor P, Petersen K. Japanese encephalitis: a review of clinical guidelines and vaccine availability in Asia. Trop Dis Travel Med Vaccines. 2015;1:11-8.
[16] Suwarba IGN, Andayani AR, Sukrata IW, Sunetra W. Japanese encephalitis incidence and its association with

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the length of stay and long-term outcome in 2015, Bali-Indonesia. Bali Med J. 2016;5:135-7.
[17] WHO. Weekly epidemiological record: Japanese encephalitis vaccines: WHO position paper. 2015;90:69-88.
[18] Erlanger TE, Weiss S, Keiser J, Utzinger J, Wiedenmayer K. Past, present, and future of Japanese encephalitis. Emerg Inf Dis. 2009;15:1-7.
[19] Direktorat Jenderal Pencegahan dan Pengendalian Penyakit Kementerian Kesehatan. Petunjuk teknis kampanye imunisasi Japanese Encephalitis. Jakarta: Kementerian Kesehatan RI; 2017.
[20] Michael BD, Solomon T. Seizures and encephalitis: clinical features, management, and potential pathophysiologic mechanisms. Epilepsia. 2012;53:63-71.
[21] Keppel HJ, Kopsky DJ. Phenytoin: 80 years young, from epilepsy to breast cancer, a remarkable molecule with multiple modes of action. J Neurol. 2017;264:1617-21.
[22] Hussein A, Abdulgalil A, Omer F, Eltoum H, Hamad A, El-Adil O, et al. Correlation between serum level of antiepileptic drugs and their side effects. Oman Med J. 2010;25:17-21.
[23] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
[24] Murayama H, Sakuma M, Takahashi Y, Morimoto T. Improving the assesment of adverse drug reactions using the Naranjo Algorithm in daily practice: The Japan Adverse Drug Events Study. Pharmacol Res Perspect. 2018;e00373:1-7.

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