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## Diagnosis and Management of Phenytoin-Induced Wavy Triple an Electrocardiographic Sign (Yasser Sign) and Hypocalcemia In a Young Epileptic Patient: A Case Report

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### Abstract

**Rationale:** Drug-induced disease is a common clinical entity associated with convulsions as an important adverse effect. Electrolyte disorders are noteworthy entities in clinical practice for instance hypocalcemia. A Wavy triple an electrocardiographic sign of hypocalcemia (Yasser sign) is a novel electrocardiographic sign linked to calcium deficiency. **Patient concerns:** A young single female patient presented to the emergency department with fits and chest pain at the critical care unit in Fraskour Central Hospital in Egypt. **Diagnosis:** After examination, evaluation, and assessment phenytoin-induced Wavy triple sign and hypocalcemia were confirmed. **Interventions:** Electrocardiography, oxygenation, monitoring for vital signs, echocardiography, and calcium injection. **Outcomes:** Dramatic disappearance of electrocardiographic Wavy triple sign and clinical hypocalcemia were recorded. **Lessons:** Identification of drug-induced disease is vital in the diagnosis decision-making of some medical problems. Phenytoin can induce Wavy triple sign and hypocalcemia. Wavy triple sign of hypocalcemia can be reversed by treating the cause without using the traditional anti-epileptic medications. Reassurance was the recommended regards phenytoin-induced Wavy triple an electrocardiographic sign and hypocalcemia that accompanied by fits.

**Keywords:** Phenytoin, Drug-induced, hypocalcemia, Wavy triple sign, Yasser sign

### Introduction

Overview: An 18-year-old single, student, Egyptian female patient presented in the emergency department with fits and chest pain. The primary objective for my case study was the presence of major fits, chest pain, and

ECG Wavy triple sign post-using phenytoin in a young girl. The secondary objective for the case study was; How would you manage phenytoin-inducing fits, Wavy triple sign, and chest pain?

Several qualitative changes due to electrolyte imbalance

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may be seen on an electrocardiogram (ECG) [1]. The QTc-interval prolongation is an old non-specific ECG finding in hypocalcemia [2,3]. This is had happened after the recent innovation of Wavy triple an electrocardiographic sign (Yasser Sign) which is a new diagnostic sign in hypocalcemia [3]. The author interpretations for this sign are based on the following-

1. Different successive three beats in the same lead are affected.
2. A Wavy triple sign can affect all ECG leads.
3. An associated elevated beat is seen with the first of the successive three beats, a depressing beat with the second beat, and an isoelectric ST-segment in the third one.
4. The elevated beat is either accompanied by ST-segment elevation or just an elevated beat above the isoelectric line.
5. Also, the depressed beat is either associated with ST-segment a depressing or just depressed beat below the isoelectric line.
6. The configuration for depressions, elevations, and isoelectricities of ST-segment for the subsequent three beats are variable from case to case. So, this arrangement is non-conditional. This is meaning the sign conditionally no affect specific ECG partition e.g., inferior, anterior, or lateral, etc. Mostly, there is no participation among the involved leads. Thus, the sign is not conditionally included in an especial coronary artery for the affected leads [3].

An adverse drug reaction (ADR) is described by the World Health Organization (WHO) as a harmful, purposeless, and undesirable drug effect when used for therapeutic objectives in humans. Anti-epileptic drugs (AEDs) have a remarkable influence on the quality of life of epileptic patients. In this regard, early detection of ADRs is important in the management of epilepsy [4].

A correlation between phenytoin and the occurrence of hypocalcemia via changing the bone and mineral metabolism was investigated. It causes augmentation in the metabolism of vitamin D and its active metabolites by

induction of the hepatic enzyme; 25 $\alpha$  hydroxylase which has a role in lowers calcium gastro-intestinal absorption resulting in hypocalcemia [5]. Phenytoin is known to increases the frequency of seizures rather than controlling seizure-related hypocalcemia. Thus, doses of phenytoin consequently increase and a vicious cycle of hypocalcemia-causing seizure happens. Another alternative mechanism is that phenytoin catabolizes the bone collagen and aggravates the calcium deficiency. Supplementation with calcium and vitamin D must be given to all patients on phenytoin to take care of bone mineral alterations caused by phenytoin. However, phenytoin can be paradoxically epileptogenic in the presence of hypocalcemia. So, phenytoin is contraindicated in the cases of hypoparathyroidism and any conditions that precipitate hypocalcemia [6]. The aim of this study in this manuscript, the author concluded that the development of triple an electrocardiographic sign (Yasser sign) and hypocalcemia may be happening after using phenytoin in an 18-year-old female girl.

## Case Presentation

An 18-year-old Egyptian female patient presented in the emergency department with fits and chest pain. The patient's relatives gave a history of past fits, the last episode having been witnessed about 1 year ago. The latest fits had happened within two hours of psychofamilial stress. The patient had no history of having used prescribed anti-epileptic drugs in the past and no incidences of cardiac, thyroid, or other relevant diseases. Upon examination, the patient appeared a major fit. Her vital signs were as follows: blood pressure of 100/70 mmHg, the pulse rate of 86/bpm; and regular, the respiratory rate of 18/min, the temperature of 36.8°C, the pulse oximeter of oxygen (O<sub>2</sub>) saturation of 95%, and tachycardia on heart auscultation. No more relevant clinical data were noted during the clinical examination regarding the epileptic scene. The initial ECG tracing on the ICU admission was taken before phenytoin loading within 30 minutes of midazolam 2.5mg amp injection showing normal sinus rhythm with VR; 88 bpm Figure 1. The patient was admitted to the ICU as an epileptic fit for management and monitoring of the vitals and O<sub>2</sub> saturation. Oxygen inhalation (5 L/min) with an O<sub>2</sub> generator was given. Diluted 5 mg/mL amp of midazolam

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in 4 ml 0.9% sodium chloride; 2.5 mg was be given over 2 minutes. The sedative effect occurred within 2 minutes. Recurrence of *epileptic fit* within 20 minutes had happened. Phenytoin sodium solution 5 ml/250mg was added with loading at 10mg/kg at 25mg/min, Then, maintenance at IV rate 50 mg/min. Serial ECG tracings were done. The second ECG tracing was taken within 3 hours of phenytoin loading showing normal sinus rhythm with Wavy triple sign of hypocalcemia (Yasser sign) in three leads of ECG (V4-6) with VR; 80 bpm Figure 2A. The patient was in tetany. Phenytoin was transiently ceased due to tetany and hypocalcemia. Two calcium gluconate ampoules (10 ml 10% over IV over 20 minutes) were given as an emergency dose. Maintenance therapy with IVI calcium gluconate ampoules (10% with the rate; 0.5 mg/kg/hour over IV over 6 hours) was infused. Re-adding phenytoin IVI after calcium gluconate stoppage with the same above maintenance dose. Tetany and hypocalcemia were immediately recurrent. Phenytoin had been ceased again due to tetany.

The third ECG tracing was taken was done within 2 hours of the second phenytoin IVI maintenance showing sinus tachycardia with Wavy triple sign in two leads of ECG (V4-5) with VR; 110 bpm. Figure 2B. Re-adding calcium gluconate IVI after phenytoin stoppage with the same above maintenance dose. The fourth ECG tracing was taken within 4 hours after calcium re-injection showing NSR with VR of 82 beats/min and the disappearance of the above Wavy triple sign Figure 2C. Plasma sodium was (137 mmol/L). Serum potassium was (4.9 mmol/L). Serum calcium showing hypocalcemia with ionized calcium; 0.25 mmol/L. The troponin test was negative (less than 2 ng/ L). Later echocardiography showed no detected abnormalities with EF 58%. The dramatic response of Wavy triple an electrocardiographic sign to calcium injection occurred. Clinical improvement of tetany and gradual reversal of laboratory hypocalcemia had happened. Serum ionized calcium after the correction was 0.88 mmol/L). The patient was discharged within 12 hours after clinical relief and electrocardiographic normalization Table 1.

Issue	After phenytoin IVI	After phenytoin cessation and IV calcium
Complaint	Fits and tetany	No complaint
Generally	An irritable	Good
Vital signs		
Blood pressure (mmHg)	100/70	110/80
Pulse rate (bpm)	86	82
Respiratory rate (bpm)	18	14
Temperature (°C)	36.8	36.5
O2 saturation (%)	95	97
ECG	NSR with Wavy triple sign of hypocalcemia (Yasser sign)	NSR with disappearance of Wavy triple sign
Serum ionized calcium	0.25 mmol/L	0.88 mmol/L

Table 1: Summary of the clinical characteristic of the patient after phenytoin IVI and post-phenytoin cessation and IV calcium. NSR; Normal sinus rhythm, O2; oxygen.

Oral calcium and vitamin-D preparation were prescribed on discharge. Future serial ionized calcium, neurologist, and nephrologist consultation was advised.



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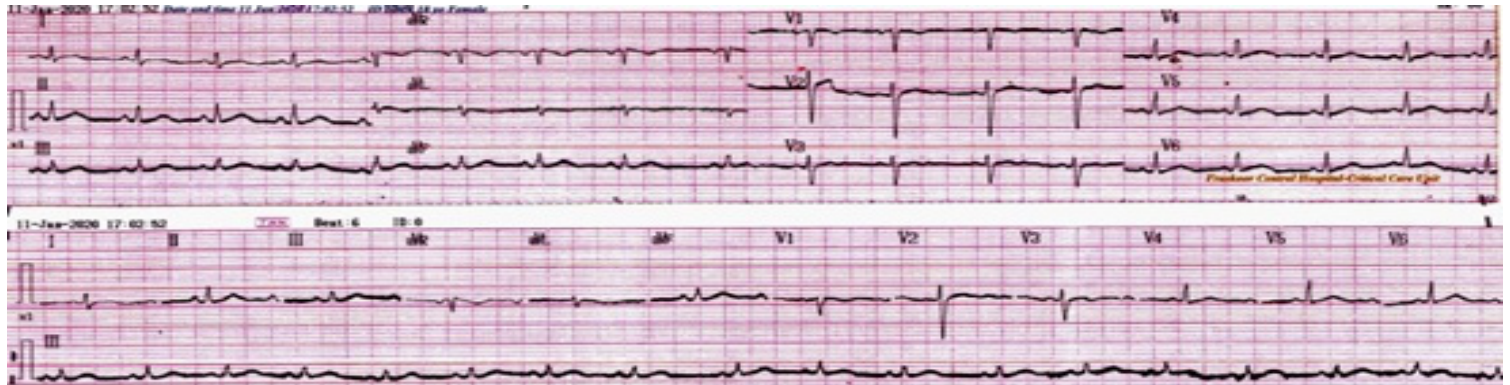


Figure 1: An initial ECG tracing on the ICU admission, before phenytoin loading, and within 30 minutes of midazolam 2.5mg amp injection showing NSR with VR; 88 bpm.



Figure 2 Serial ECG tracings (A): An initial ECG tracing was done within 3 hours of phenytoin loading showing NSR with Wavy triple sign of hypocalcemia (Yasser sign) in three leads of ECG V4-6) with VR; 80 bpm. Red arrows indicate an elevated beat.



Figure 2 Serial ECG tracings (B): ECG tracing was done within 2 hours of the second phenytoin IVI maintenance showing sinus tachycardia with Wavy triple sign in two leads of ECG (V4-5) of VR; 110 bpm. Green arrows indicate a depressing beat. Blue arrows indicate an isoelectric beat.

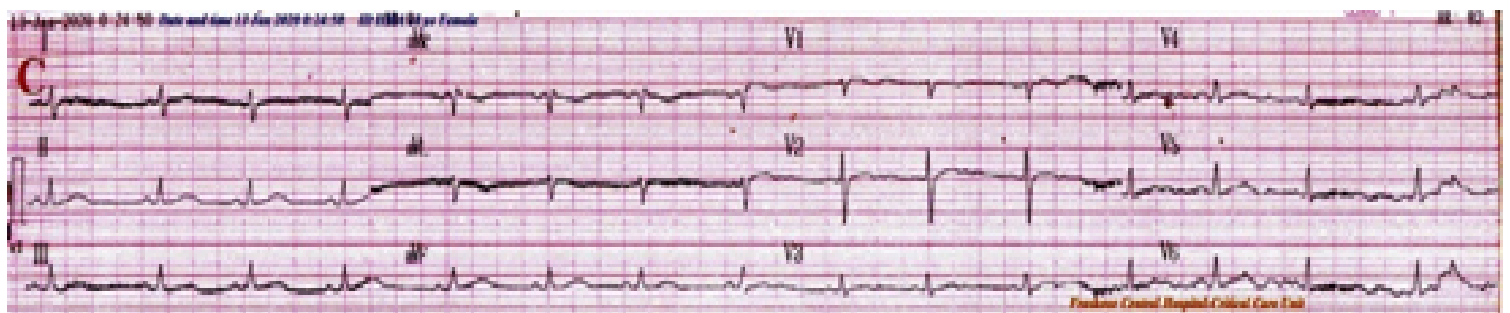


Figure 2 Serial ECG tracings (C): ECG tracing within 4 hours after calcium re-injection showing NSR with VR of 82 beats/min and the disappearance of above Wavy triple sign.

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## Discussion

The dramatic reversal of the Wavy triple sign after calcium gluconate injection suggests that these signs were due to phenytoin inducing hypocalcemia. Phenytoin inducing Wavy triple sign and hypocalcemia can be reversed with calcium injection without using anti-epileptic drugs. Indeed, the mechanism of phenytoin inducing Wavy triple an electrocardiographic sign (Yasser sign) and hypocalcemia is unknown. Phenytoin is known to cause hypocalcemia by altering bone and mineral metabolism. It increases the metabolism of vitamin D and its active metabolites by hepatic enzyme (25 $\alpha$  hydroxylase) induction, which in turn lowers the calcium absorption from the gut and causes hypocalcemia [5,6]. The author thinks that psychogenic hyperventilation syndrome [7,8] and malnutrition [9, 10] may be trigger factors. The negative troponin test with non-conclusive ECG changes for ischemic heart disease (IHD), and normal echocardiography will quietly exclude the presence of IHD. Despite the drug-drug interactions (DDIs) or even drug-food interactions have a strong impact in inducing various serious drug adverse effects, but it was unviable in my case report. Absent of using drug combinations in the patient history may exclude the theory of drug-drug interactions. Finally, I reported the development of Wavy triple an electrocardiographic sign (Yasser sign) and hypocalcemia within 3 hours after using phenytoin in an 18-year-old female girl. The main differential diagnoses for the study case are ischemic heart disease. In ischemic heart disease, ST-segment affects all beats in ECG by either elevation or depression. But, in the Wavy triple sign, there are subsequent three beats of elevated, depressed, and isoelectric criteria. The only limitation of the study was the unavailability of serum level of phenytoin to follow up the toxicity level and management. This is the first case that reports these adverse drug reactions with phenytoin. So, I can't compare this case with another case because there was no similar publicized case report. After the exclusion of other possible triggers in the current case, the Naranjo probability scale [9] was used to evaluates the association between phenytoin and the development of Wavy triple sign with hypocalcemia. Naranjo's probability scale in the current case study was +10. It is meaning that there was a definite relationship between these adverse drug reactions and the causing drug; phenytoin. The drug-induced

disease is a pivotal step in the diagnosis decision-making of any medical problems. Drug side effects are a sometimes-strong way for the diagnostic challenge in clinical medicine.

## Conclusions

The dramatic disappearance of Wavy triple an electrocardiographic sign (Yasser sign) after calcium injection in the patient using phenytoin is meaning that this sign was lonely due to phenytoin. Phenytoin can induce Wavy triple an ECG sign and hypocalcemia. The author thinks that Wavy triple sign and hypocalcemia can be reversed with treatment of the cause without using anti-epileptic drugs. Future precautions on using phenytoin; specifically, or anti-epileptic drugs in general are the recommendation for the current case study.

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## Conflicts of Interest

There are no conflicts of interest.

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