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Research Article

Wavy Triple an Electrocardiographic Sign (Yasser Sign) in Hypocalcaemia-A Novel Diagnostic Sign; Retrospective Observational Study

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Received: October 26, 2019; **Published:** November 06, 2019

Abstract

Background: Hypocalcemia is a well known serious electrolyte disturbance characterized by calcium deficiency. It is associated with non-specific electrocardiographic changes.

Method of Study and Patients: My case study was an observational retrospective 25-case report series. The study was conducted in both Fraskour Central Hospital and (in both the Emergency Department, Internal Ward and Intensive Care Unit) and Physician Outpatient Clinic. The author reported the 37-cases thorough nearly 15-months, started from March 12, 2018 and, ended on June 08, 2019. Tetany or latent hypocalcemia are included. Parenteral or oral calcium preparation was supplied.

Results: The Mean age was: 38.4 years, with female sex predominance (72.97%). Hyperventilation syndrome (45.95%) and malnutrition (24.32%) are the most common risk factors. Carpopedal spasm was the main complaint (89.19%). Manifested tetany was the commonest final diagnosis (89.19%). Wavy triple sign is a positive and triple sign in 97.3% (36 cases) but it is only double in 2.7% (1 case). The Mean number of affected electrocardiographic leads: 4.13, Max.:10 and Min.:1). The number of affected ECG leads correlate with the level of ionized calcium in the investigated group. Electrocardiographic recovery after calcium administration in the first group was completed in 97.3% vs. partial in 2.7%.

Conclusion: The wavy triple an electrocardiographic sign (Yasser sign) is a new diagnostic sign seen in 97.3% (36 cases) of hypocalcemia. Dramatic improvement of both clinical manifestation and the new electrocardiographic sign simultaneously after calcium replacement had happened.

Keywords: *Wavy Triple an Electrocardiographic Sign; Yasser Sign in Hypocalcemia; Hypocalcemia; Tetany*

Abbreviations

ABG: Arterial Blood Gases; ATP: Adenosine Triphosphate; Ca: Calcium; CPU: Cardiopulmonary Bypass ECG: Electrocardiographic; ED: Emergency Department; ICU: Intensive Care Unit; IV: Intravenous; IW: Internal Ward; POC: Physician Outpatient Clinic; RBS: Random Blood Sugar

Introduction

Historical bit and hypocalcemic definition

The term of tetany especially the latent type was introduced in the medical literature since 1945 [1-3]. Epidemiologic studies regard hypocalcemia versus other electrolyte disorders have not been executed. Over the last decades, laboratory tests have quantified serum and ionized calcium (Ca^{++}) and PTH levels permitted easier diagnosis [4]. Hypocalcemia is a common state characterized by a net loss of calcium from the extra-cellular fluid (ECF) in large amounts than can be restored by the intestine or bone [5,6]. Hypocalcemia is a prevalent biochemical disorder that can vary in severity from being asymptomatic in mild cases to presenting as an acute fatal crisis [7,8].

Calcium and its metabolic role

Calcium plays an essential in the cellular mechanisms of myocardial contraction [7,9]. Calcium has a pivotal and structural role in the maintenance of myocardial function, cardiac output and vascular tone [10]. The calcium ion is important in several biological processes that include cardiac automaticity; excitation with contraction coupling in myocardial, smooth and skeletal muscle; blood coagulation; neuronal conduction; synaptic transmission; hormone secretion and mitotic division. Calcium is also a crucial intracellular messenger necessary for normal cellular function and in demand for many enzymes fully activity [5]. Calcium can have a fundamental role in tissues and organ injury after ischemia, hypoxia, reperfusion and toxic cell death. At the cellular level, there is Ca^{++} influx in response to these insults, leading to intracellular Ca^{++} overload, which may cause cellular injury in many directions: A. Stimulation of calcium-dependent lipases, proteases and nucleases. B. Increase in free radical production. C. Increase in adenosine triphosphate (ATP) consumption via calcium-ATPases. E. And inhibition of mitochondrial ATP generation by uncoupling of oxidative phosphorylation. Cell death then follows as a result of this intracellular insults [10]. Contraction of all smooth-muscles is dependent on changes in the intracellular Ca^{++} level. This is due to inherent myogenic mechanisms that regularly depolarize the muscle fibers or from neural or hormonal actions. As a result of a rise in the cytoplasmic concentration of Ca^{++}, more Ca^{++} combines with the calmodulin regulatory protein to stimulate a protein kinase that phosphorylates myosin with succeeding stimulation of the smooth muscle actin ± myosin complex [5]. Serum Ca^{++} levels are regulated within a narrow range (2.1 to 2.6 mmol/L) by three main calcium-regulating hormones; parathyroid hormone (PTH), vitamin D and calcitonin, through their specific effects on the bowel, kidneys and skeleton [11,12]. About 50% of the total serum Ca^{++} is protein-bound and the remaining free ionized calcium is physiologically active [12]. So, serum calcium levels should be corrected for the albumin level before confirming the diagnosis of hypercalcemia or hypocalcaemia [11].

The ionized calcium

The ionized Ca^{++} is the major physiological part that needs to be checked to evaluate physiologically active calcium levels [10]. Total Ca^{++} in serum (8.8 to 10.4 mg/dl) includes free ions, ions bound to albumin, with small extent is another diffusible complexes. The concentration of free calcium ions, averaging 4.8 mg/dl, influences many cellular functions and is subjected to tight hormonal control, especially through PTH. In a patient with hypocalcemia, the serum albumin is essential to the diagnosis of true hypocalcemia which involves a reduction in ionized serum Ca^{++}, or to the diagnosis of "factitious" hypocalcemia, meaning decreased total, but not ionized, Ca^{++} [13]. Ionized calcium has a central role in regulating myocardial contraction. During the cardiac action potential is activated, ionized Ca^{++} enter intracellular through depolarization activated Ca^{++} channels. Entered ionized calcium triggers calcium release from the sarcoplasmic reticulum (SR). Ca2+ bind to the myofilaments proteins such as troponin C initiate contraction of myocardium [9,14]. The free ionized Ca^{++} is the physiologically important component of the total calcium. In plasma, the ionized calcium concentration is normally maintained within a narrow range (1.0 ± 1.25 mmol), despite a widely varying input of Ca^{++} from the intestine and bone. Maintenance within this range is accomplished mainly by the action of three main calciotropic hormones: parathyroid hormone, calcitriol (1,25-dihydroxy-vitamin D) and calcitonin[5]. Life-threatening complications frequently occur if the serum ionized Ca^{++} concentration decreases to below 2 mg/d [5]. The poorer prognosis was reported in those patients with ionized hypocalcemia [10]. Calcium giving to the patients with severe ionized hypocalcemia (>30% decrease) can lead to a marked improvement in cardiac output [10].

Etiology of hypocalcemia

Hypoparathyroidism, vitamin D deficiency and hypoalbuminemia are the commonest implicated causes of hypocalcemia [4,8]. Others causes include: Eating disorders, renal disease or end-stage liver disease causing vitamin D deficiency, pseudohypoparathyroidism or pseudopseudohypoparathyroidism, metastatic or heavy metal such as copper, iron, parathyroid gland infiltration, hypomagnesaemia or hypermagnesemia, sclerotic metastases, Hungry bone syndrome post-parathyroidectomy, phosphate infusion, citrated massive transfusions, acute critical illness, Fanconi syndrome, post-radiation of parathyroid glands, renal failure, acute pancreatitis, calcium blocker toxicity, rhabdomyolysis, tumor lysis syndrome, nutritional defect [4,6-8].drug-induced such as cinacalcet [15]. 5-fluorouracil with leucovorin [16], high-dose of intravenous zoledronic acid [6-8,17], acid phenobarbital [18], phenytoin [18], denosumab [19], foscarnet [4] and sodium phosphate preparations [20,21]. Falsely low levels of calcium due to hypoalbuminemia should be excluded by measuring ionized calcium [5]. Ionized hypocalcemia frequently occurs in many clinical situations, including sepsis, pancreatitis, hypomagnesemia, following large blood transfusions, After neck surgery, after cessation of cardiopulmonary bypass (CPU) in cardiac surgery and after Initiation of extracorporeal membrane oxygenation [10]. The symptoms generally correlate with the magnitude and rapidity of the decrease in serum calcium [5]. Fatal complications frequently occur if the serum ionized Ca^{++} concentration decreases to below 2 mg/d [5]. Alkalosis that induced by hyperventilation, hypokalemia, epinephrine, post-emotional stress and hypomagnesemia may aggravate the symptoms of hypocalcemia; but acidosis decreases symptoms, especially in chronic renal failure who often tolerate significant hypocalcemia without complaining of symptoms [13,22].

Clinical impact of hypocalcemia and diagnosis

Acute hypocalcemia can result in severe symptoms requiring hospitalization [8,9,11]. whereas patients who gradually develop hypocalcemia are more likely to be asymptomatic [8,9,11]. Severe hypocalcemia or the quick happening of hypocalcemia may accompany with Chvostek and Trousseau's sign [9]. Hypocalcemia may present with a variety of clinical signs and symptoms; include paresthesia, muscle spasms, cramps, fatigue, weakness, tetany, circumoral numbness, convulsions, laryngospasm, bronchospasm, hypotension, bradycardia, digitalis insensitivity, arrhythmias, heart failure, cardiac arrest, hyperactive reflexes, neuromuscular irritability, cognitive impairment and personality disturbances [5,6,8,11,12,23]. The tingling sensation is the hallmark symptom of hypocalcemia [9]. The diagnosis of latent tetany is depending on the clinical signs that associated with hypocalcemia; the presence of Chvostek or Trousseau signs. The term "latent tetany" is extremely ambiguous [5]. Chvostek and Trousseau signs can be induced in cases of hypocalcemia [6,8]. Diagnosis should generally be confirmed with corrected calcium or ionized calcium level [8].

Hypocalcaemia and cardiovascular system

Acute hypocalcemia is an inducer for syncope, congestive heart failure (CHF) and angina due to the several cardiovascular effects [24]. The hemodynamic effect of calcium administration may be different in the presence of hypocalcemia [10]. Calcium administration to patients with severe ionized hypocalcemia (>30% decrease) can lead to a significant improvement in cardiac output [10]. Calcium supplementation may correct a biochemical abnormality and thereby improve cardiovascular status; in contrast, excessive calcium influx into the cells may contribute to cellular damage associated with hypoxia [10]. Severe extracellular (EC) hypocalcemia impair cardiac contractility because the sarcoplasmic reticulum is unable to maintain a sufficient amount of calcium content to initiate myocardial contraction [9]. The cell membrane potential is lower in the condition of hypocalcemia, which increases cell membrane permeability and muscle enzyme is leakage from the cells [25]. However, the elevated cardiac enzyme usually returns to normal after treatment of hypocalcemia [9]. Severe ionized hypocalcemia (≤40 - 50% of normal) is associated with reduced ventricular contractility, bradycardia and impaired vascular tone, leading to arterial hypotension [10]. Animal studies had established a positive relationship between serum calcium levels and arterial blood pressure [10].

ECG in hypocalcemia

Specific changes may be seen on an electrocardiogram (ECG) [26]. It is important to note that the electrocardiogram may be normal during life-threatening hypocalcemia and a normal ECG cannot, therefore, be relied upon to exclude this condition [5]. The ECG hallmark of hypocalcemia remains the prolongation of the QTc interval because of lengthening of the ST segment, which is directly proportional to the degree of hypocalcemia or, as otherwise stated, inversely proportional to the serum calcium level [27]. Hypocalcemia is a cause of QTc prolongation and this predisposes to ventricular arrhythmias [28]. This causes calcium ion channels to remain open for a longer period, allowing a late calcium inflow and the formation of early after-depolarization [29,30]. If the threshold for depolarization is reached, new action potentials are induced, initiating a tachycardia and re-entry. Ventricular arrhythmias can follow, in particular, torsades de pointes (TdP) and ventricular fibrillation (VF) [31]. Therefore, ventricular arrhythmias are a known complication of hypocalcemia and patients can present with exertional syncope representing TdP and loss of cardiac output [30-32].

Prolonged of both QT and ST-intervals, T inversion, bradycardia ST elevation that mimic myocardial infarction are the ECG changes which seen with hypocalcemia [5,8]. The most likely cause of the dramatic ECG abnormalities as being due to coronary vasospasm [33]. The T-waves are normal in 50% of patients, but decreased T-wave voltage and even negative to deeply negative T-waves have been said to occur [34]. Hypocalcemia generally does not cause T-wave changes because it does not affect phase 3 of the action potential. Since these changes have been reported, however, it is best to evaluate each individual for some additional coexisting process if ST-segment or T-wave changes are noted on the ECG, as was done in this case. This holds especially if there is persistent evidence for myocardial injury [27]. However, the T-wave becomes low, flat, or sharply inverted in leads with an upright QRS-complex [35]. Changes in the contour of the T-waves may be observed in all patients [34]. In patients with a prolonged QT-interval due to hypocalcemia, the U-wave is usually absent or not recognizable [35].

Hypocalcemia cause not only heart failure but also elevating cardiac enzyme and ST-segment changes in ECG which mimics with acute myocardial infarction [36]. Hypocalcemia causes QTc prolongation primarily by prolonging the ST-segment [28]. Hypocalcemia is a recognized cause of QT prolongation via prolongation of the plateau phase of the cardiac action potential [34,37]. Note, however, that patients may have clinically significant hypocalcemia or hypercalcemia without diagnostic ECG changes [35]. Considerable controversy still exists concerning other ECG abnormalities [34].

Workup in hypocalcemia

Prior to initiating correction for hypocalcemia in the emergency room, it is most important to obtain not just the serum Ca^{++} levels but, to determine serum albumin, magnesium, phosphate levels and arterial blood gas analysis to correctly diagnose and treat the underlying electrolyte abnormalities. Calcium replacement may be started without waiting for all these results if the patient has serious neuromuscular complications of hypocalcemia, e.g., seizures, bronchospasm, laryngospasm, cardiac arrhythmias [13]. The ECG is indicated. Imaging studies may include plain radiography or computed tomography (CT) scans. On radiographs, disorders associated with rickets or osteomalacia present [4]. Ionized calcium is the definitive method for diagnosing hypocalcemia. A serum Ca^{++} level less than 8.5 mg/dL or an ionized calcium level less than 1.0 mmol/L is considered hypocalcemia [4].

Prognostic value

Depending on the cause, unrecognized or poorly treated hypocalcemic emergencies can lead to significant morbidity or death [38]. Ionized hypocalcemia can be seen frequently in critically-ill patients [10]. The poorer prognosis was observed in those patients with ionized hypocalcemia [10].

Hypomagnesaemia and differential diagnosis

It is important to note that hypomagnesemia may present with the same constellation of symptoms and signs. Hence, ideally, serum magnesium levels should also be measured in each patient having these symptoms. Sustained correction of hypocalcemia cannot be achieved by administration of calcium alone in patients of hypomagnesemia; instead, administration of magnesium corrects the hypocalcemia in such patients [13]. The symptoms and signs of hypocalcemia are quite evident when the hypocalcemia is profound or occurs acutely [13]. Chronic hypocalcemia is associated with milder symptoms and signs of neuromuscular irritability and may even be asymptomatic [22] (in which case latent tetany may be elicited by the Chvostek, Trousseau or Erb sign) [13]. Coexisting hypomagnesemia (serum Mg levels < 1.8 mg/dl) should be considered in every patient and if present or if the magnesium status is unknown, magnesium should be supplemented [13,39]. Severe hypomagnesemia can lead to hypocalcemia that is resistant to the administration of calcium and vitamin D [4].

Acute management of hypocalcemia

Management should comprise of suspecting that the patient's symptoms and signs may be caused by hypocalcemia [13]. The treatment of hypocalcemia depends on the cause, the severity, the presence of symptoms and how rapidly the hypocalcemia developed [4]. Most hypocalcemic emergencies are mild and require only supportive treatment and further laboratory evaluation [4]. Intravenous calcium is given if serum calcium levels fall below 1.9 mmol/L, or ionized calcium levels are less than 1 mmol/L, or if patients are symptomatic [8]. Patients should also receive oral calcium supplements and calcitriol (0.25 to 1 μg/day) as needed [8]. Oral calcium and vitamin D and its metabolites are essential in management, in addition to correction of hypomagnesemia [13]. Cholecalciferol is more potent than ergocalciferol. Calcium supplementation may correct a biochemical abnormality and thereby improve cardiovascular status; in contrast, excessive calcium influx into the cells may contribute to cellular damage associated with hypoxia [10]. Supplementation of calcium in hypocalcemic patients may be associated with hemodynamic improvement [10]. Calcium administration to patients with severe ionized hypocalcemia (> 30% decrease) can lead to a significant improvement in cardiac output [10]. Correction of serum level of calcium did not sufficient for restoration of myocardial function [9]. Serum level of hypocalcemia was corrected within several days after calcium supplement [9]. However, no formula has proved accurate for assessment of serum calcium concentration in acutely ill patients [13].

Initiating emergency calcium replacement (if warranted, this can be the second step, without waiting for the serum Ca^{++} levels [13]. It is thus more useful to measure serum-free Ca^{++} ion levels using calcium electrodes. If ionized calcium cannot be measured, an approximation can be used to estimate the protein-bound and ionized fractions [13]. Consequently, ionized Ca^{++} should be measured when the diagnosis is considered in the setting of acute illness or severe hypoalbuminemia [13].

A formula [13] that estimates the amount of calcium bound to protein is:

% protein-bound Ca = 8 (albumin, g/dl) + 2 (globulin, g/dl) + 3 [13].

Studies of hypoalbuminemic patients have led to a correction that is used to determine the corrected serum calcium levels in such patients. The correction is to add 1 mg/dl to the serum calcium level for every 1 g/dl by which the serum albumin is below 4 g/dl [13]. Patients with acute symptomatic hypocalcemia (serum calcium usually below 7.0 mg/dl and ionized calcium usually below 3.2 mg/dl) should be treated promptly with IV calcium [39]. Calcium gluconate is preferred over calcium chloride because it causes less tissue necrosis if extravasated. The first 100 to 200 mg of elemental calcium (1 - 2 ampoules of 10% calcium gluconate [93 mg/10 ml ampoule]) should be given over 10 to 20 minutes. Calcium for infusion should be diluted in 50 to 100 ml of saline or dextrose solution to avoid vein irritation [13]. Calcium carbonate and calcium citrate have the greatest proportion of elemental calcium (40% and 28%, respectively) and are easily absorbed; they are considered the supplements of choice [23,40,41]. Calcium supplement dosages are 1 to 2g of elemental calcium 3 times daily (level III evidence) [23]. Elemental calcium supplements can be started at 500 to 1000 mg 3 times daily and titrated upward (level

III evidence) [23]. Asymptomatic ECG changes usually normalize with calcium and calcitriol supplementation (level II evidence) [42]. Intravenous calcium is given if serum calcium levels fall below 1.9 mmol/L, or ionized calcium levels are less than 1 mmol/L, or if patients are symptomatic (level III evidence) [11,12,43]. Rapid correction of hypocalcemia can contribute to cardiac arrhythmia [11,45]. Cardiac monitoring during intravenous calcium supplementation is necessary, particularly in patients taking digoxin therapy (level III evidence) [11,23,45]. Intravenous calcium administration restores normal polarity transiently in patients with negative T waves [46]. Long-term therapy results in permanent normalization of the ECG [46]. The marked improvements of the ECG abnormalities following replacement of calcium and vitamin D [33].

Methods and Patients

Case presentations

My study was an observational retrospective study for 37-case report series of hypocalcemia. Manifested tetany and latent hypocalcemia are included. The author reported the 37-cases of over nearly 15-months, started from March 12, 2018 and, ended on June 8, 2019. The study was conducted in both Fraskour Central Hospital and (in both the Emergency Department "ED", Internal Ward "IW" and Intensive Care Unit "ICU") and Physician Outpatient Clinic (POC). The patients divided into two groups. The first group comprises only fifteen patients of investigated hypocalcemia that were undergoing to both serial ECG before and after calcium administration. This group also investigated for total and ionized calcium and other electrolytes before and after calcium administration. Random blood sugar was done for all cases. Arterial blood gases, troponin test, serum albumin and echocardiography were done in selected cases. Most of the cases were admitted in the internal ward. Few cases either admitted or present in the ICU. The remaining cases were managed in POC with later follow up. The second group comprises twenty-two patients of investigated hypocalcemia only undergoing the initial ECG before calcium administration. ECGs are initially examined for the new sign-in hypocalcemia; "Wavy Triple an Electrocardiographic Sign (Yasser Sign)" (Figure 1). This group not undergoing any investigations. In this group, just the patients clinically improved from tetany, the author missed them. Initial parenteral or later oral calcium preparation was supplied. Only one to two calcium gluconate ampoule 10 ml 10% over IV over10 - 20 minutes were the taken emergency doses in the study. Initial oral calcium preparation was only supplied for mild cases or cases of latent tetany. The oral calcium and vitamin-D preparation were supplied after discharge for all the cases. For more details on general, clinical and laboratory data for the cases see (Table 1 and 2).

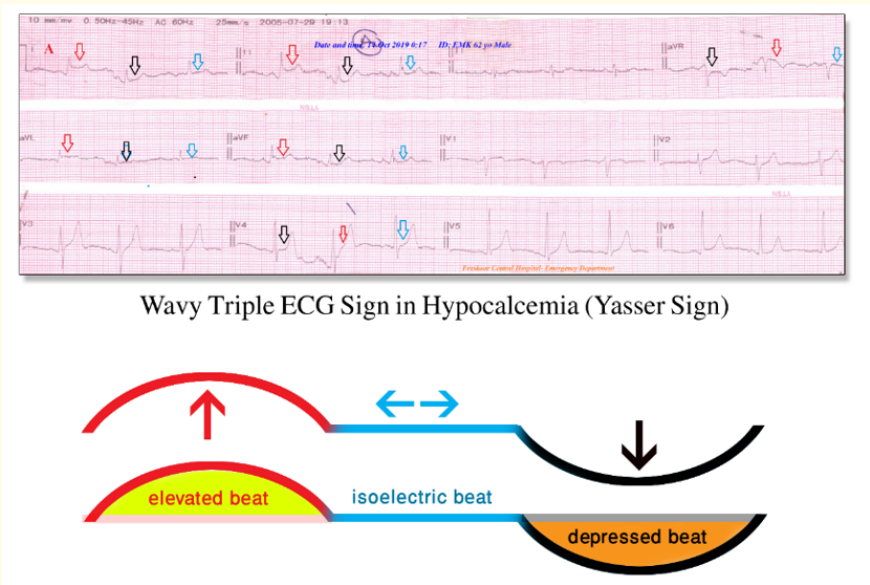

Figure 1: *Author caricaturing diagrammatic clarification with a case example for "wavy triple sign". Red arrow =elevated beat, blue arrow = isoelectric beat, black arrow = depressed beat.*

Case No.	Age Per year	Sex	The main complaints	BP mg Hg	Pulse bpm	RR	Associated RF	Severity	Number of affected ECG leads	Number of given CA amp.	Final diagnosis	Outcome (Response to Ca^{++})
1.	28	F	Carpopedal spasm	100/70	75	18	Malnutrition	Severe	10	2	Manifested tetany	Clinical+ECG
2.	26	F	Carpopedal spasm	100/80	82	16	Malnutrition	Mild	6	1	Manifested tetany	Clinical+ECG
3.	63	M	Carpopedal spasm	110/60	65	14	Malnutrition	Severe	6	2	Manifested tetany	Clinical+ECG
4.	30	F	Carpopedal spasm	100/60	70	30	HVS	Severe	3	2	Manifested tetany	Clinical+ECG
5.	42	F	Carpopedal spasm	99/70	82	36	HVS	Mild	3	1	Manifested tetany	Clinical+ECG
6.	65	M	Carpopedal spasm	110/80	78	26	DKA, CLD	Mild	6	1	Manifested tetany	Clinical+ECG
7.	30	F	Carpopedal spasm	90/60	90	34	HVS	Severe	3	2	Manifested tetany	Clinical+ECG
8.	58	M	Carpopedal spasm	100/70	92	14	Malnut. CLD	Mild	6	2	Manifested tetany	Clinical+ECG
9.	75	F	CVA+HVS	150/90	150	32	HVS, CVA	Severe	3	2	Accidentally Dx	Clinical+ECG
10.	29	F	Parathesia, tingling	130/70	88	16	Malnutrition	Mild	2	Oral Ca	Latent tetany	Clinical+ECG
11.	20	F	Carpopedal spasm	100/60	82	28	HVS	Mild	2	1	Manifested tetany	Clinical+ECG
12.	50	F	Carpopedal spasm	90/70	76	14	Malnutrition	Severe	6	2	Manifested tetany	Clinical+ECG
13.	13	F	Carpopedal spasm	110/80	105	32	HVS	Severe	8	2	Manifested tetany	Clinical+ECG
14.	39	F	Carpopedal spasm	90/80	65	38	HVS	Mild	4	1	Manifested tetany	Clinical+ECG
15.	53	F	Carpopedal spasm	100/60	84	12	Malnutrition	Severe	5	2	Manifested tetany	Clinical+ECG
16.	43	F	Carpopedal spasm	90/60	92	26	HVS	Severe	4	2	Manifested tetany	Clinical*
17.	57	M	Carpopedal spasm	150/90	76	14	Malnut. CLD	Severe	5	2	Manifested tetany	Clinical*
18.	33	F	Carpopedal spasm	110/60	94	26	HVS	Mild	2	1	Manifested tetany	Clinical*
19.	30	F	Carpopedal spasm	100/70	98	34	HVS	Mild	3	1	Manifested tetany	Clinical*
20.	37	F	Carpopedal spasm	90/60	88	28	HVS, Coffee	Mild	3	1	Manifested tetany	Clinical*
21.	89	M	Parathesia, tingling	110/60	86	14	Malnut. Elder	Mild	2	Oral Ca	Latent tetany	Clinical*
22.	23	F	Carpopedal spasm	90/60	80	24	HVS, Pregn.	Mild	1	1	Manifested tetany	Clinical*
23.	30	F	Carpopedal spasm	110/70	130	26	HVS	Mild	1	1	Manifested tetany	Clinical*
24.	23	M	Carpopedal spasm	130/80	100	34	HVS,Addict**	Severe	4	2	Manifested tetany	Clinical*
25.	25	F	Carpopedal spasm	90/70	120	34	HVS	Mild	2	1	Manifested tetany	Clinical*
26.	17	F	Carpopedal spasm	110/60	86	38	HVS	Severe	4	2	Manifested tetany	Clinical*
27.	34	F	Carpopedal spasm	80/60	106	30	HVS DKA	Mild	3	1	Manifested tetany	Clinical*
28.	33	F	Carpopedal spasm	90/70	90	32	HVS-Pregn.	Mild	3	1	Manifested tetany	Clinical*
29.	26	F	Carpopedal spasm	100/60	94	14	Malnutrition	Mild	3	1	Manifested tetany	Clinical*
30.	18	F	Carpopedal spasm	100/70	98	34	HVS	Severe	9	2	Manifested tetany	Clinical*
31.	28	M	Carpopedal spasm	110/80	98	32	HVS	Severe	6	2	Manifested tetany	Clinical*
32.	21	M	Carpopedal spasm	100/70	76	26	HVS	Mild	3	1	Manifested tetany	Clinical*
33.	40	F	Carpopedal spasm	90/60	78	30	HVS	Severe	7	2	Manifested tetany	Clinical*
34.	60	M	Carpopedal spasm	110/70	86	16	Malnutrition	Mild	3	1	Manifested tetany	Clinical*
35.	57	M	Carpopedal spasm	130/90	66	28	HVS	Mild	3	1	Manifested tetany	Clinical*
36.	30	F	Carpopedal spasm	120/70	94	14	Malnutrition	Mild	3	1	Manifested tetany	Clinical*
37.	46	F	Parathesia, tingling	110/80	76	26	HVS, Coffee	Mild	4	Oral Ca	Latent tetany	Clinical*

Table 1: *Summary of the history, clinical, and management Data for all the study cases.*

** (no follow up with ECG), Addict**; Marijuana, BP: Blood Pressure; Ca: Calcium; CLD: Chronic Liver Diseases; CVA: Cerebrovascular Accident; DKA: Diabetic Ketoacidosis; ECG: Electrocardiography; F: Female; HVS: Hyperventilation Syndrome; K^{+}: Potassium: Mg^{++}: Magnesium; M: Male; Malnut: Malnutrition; Na^{+}: Sodium; Pregn: Pregnancy; RA: Risk Factor; RR; Respiratory Rate.*

Case no.	Ionized Ca^{++} mg/dl	Total Ca^{++} mg/dl	Na^{+} mg/dl	K^{+} mg/dl	Mg^{++} mg/dl	S creatinine mg/dl	RBS mg/dl	S albumin mg/dl	ABG	Troponin test
1	4.5	8	142	4	2.3	1.2	98	4	RA^{*}	-
2	4.5	8.3	137	5.1	2	1.1	112	.3.7	-	-
3	4.1	7.5	139	5.3	2.1	0.9	91	3.6	-	-VE
4	4.5	8	142	4	2.3	1.1	98	4	RA	-
5	4.4	8.1	139	4.2	2	0.9	123	3.9	N	-
6	4.2	7.7	134	3.6	1.9	1.6	532 (DKA)	2.1	MA^{**}	-VE
7	3.9	7.8	143	3.9	2.1	0.9	88	3.8	RA	-
8	4.5	8.4	137	4.1	1.9	1.1	94	3.4	-	-VE
9	3.9	7	144	3.9	2.1	1.5	186	3.6	RA	-VE
10	4.4	7.9	141	4.6	1.8	1.3	108	4.3	N	-
11	4	7.3	138	4.5	2	1	117	4.2	RA	-
12	3.8	7.1	136	4.9	1.9	0.9	105	3.7	-	-VE
13	3.6	7	138	4.3	2.1	1	99	4.2	RA	-
14	4.5	8.4	137	4.5	2	0.9	86	3.7	N	-
15	3.9	7.6	140	4.7	1.9	1	102	3.8	-	-VE

Table 2: *Laboratory data for the cases of the first group.*

ABG: Arterial Blood Gases; BP: Blood Pressure; Ca^{++}: Calcium; CLD: Chronic Liver Disease; CVA: Cerebrovascular Accident; D: Deficiency; DKA: Diabetic Ketoacidosis; Diagnosis; HR: Heart Rate; HVS: Hyperventilation Syndrome; MA^{**}: Metabolic Acidosis; Na^{+}: Sodium; K^{+}: Potassium; Mg^{++}: Magnesium; RR: Respiratory Rate; RA: Respiratory Alkalosis; RBS: Random Blood Sugar.

Case No. 1: A 28-year-old married Egyptian housewife female patient presented to ED with carpopedal spasm. The patient gave a recent history of poor nutritional status due to psycho-social troubles. Two-calcium gluconate ampoules 10 ml 10% over IV over 20-minutes were taken. Complete clinical and electrocardiographic recovery (Figure 2).

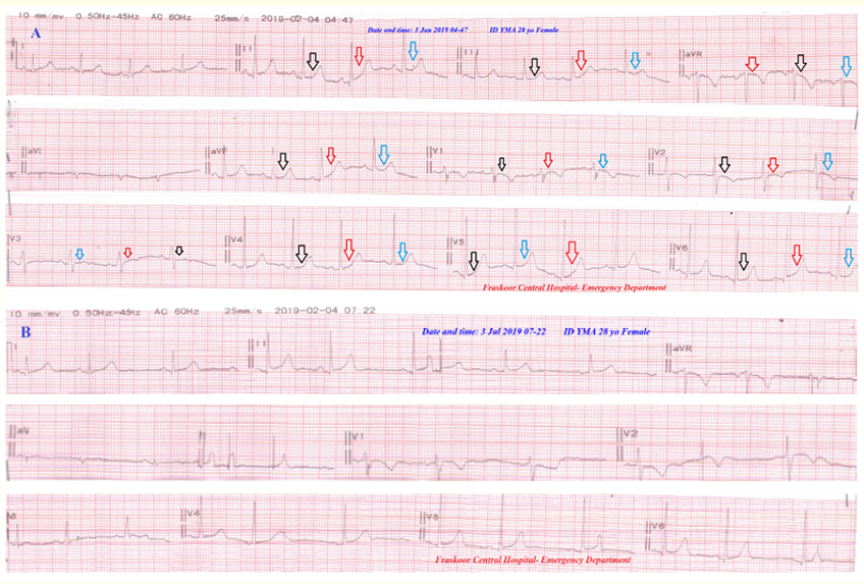

Figure 2: *A-ECG tracing of the presentation showing "Wavy triple sign" in Leads: I, II, III, aVF, aVR and V1-6. (red arrows =elevated beats, blue arrows = isoelectric beats and black arrows =depressed beat). B-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 2: A 26-year-old married Egyptian housewife female patient presented to the POC with carpopedal spasm and psychogenic hyperventilation syndrome. The patient gave a recent history of poor nutritional status due to poor status. One-calcium gluconate ampoule 10 ml 10% over IV over 10 minutes was taken. Complete clinical and electrocardiographic recovery (Figure 3).

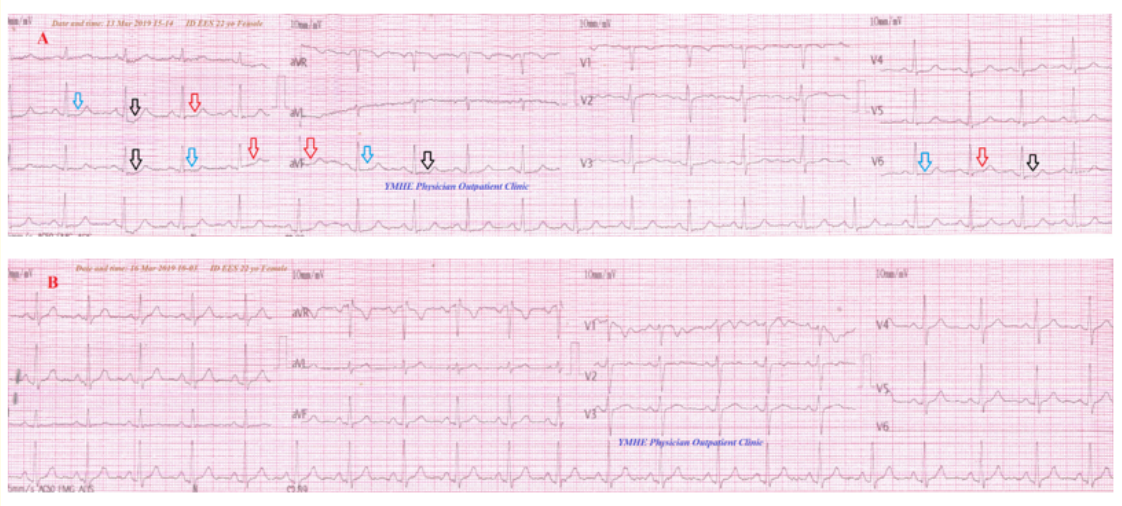

Figure 3: *A-ECG tracing of the presentation showing "Wavy triple sign" in Leads: II, III, aVF and V6. (red arrows =elevated beats, blue arrows = isoelectric beats and black arrows =depressed beat). B-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 3: A 63-year-old married Egyptian male farmer patient presented to the ED with carpopedal spasm. The patient gave a recent history of poor nutritional status due to deprivation. The patient was admitted in the internal ward as tetany. Two-calcium gluconate ampoules 10 ml 10% over IV over 20-minutes were taken. Complete clinical and electrocardiographic recovery (Figure 4).

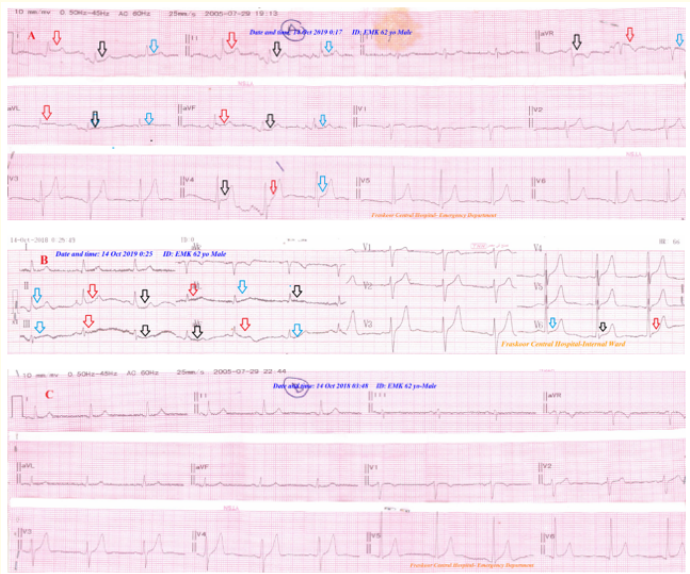

Figure 4: *A-ECG tracing of the ED presentation showing "Wavy triple sign" in Leads: I, II, aVF, aVR, aVL and V4. B-ECG tracing of IW copy before CA administration showing some changes of the wavy sign in Leads II, III, aVL, aVF and V6. (red arrows =elevated beats, blue arrows = isoelectric beats, and black arrows = depressed beats). C-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 4: A 30-year-old married Egyptian housewife female patient presented to the ED with carpopedal spasm and psychogenic hyperventilation syndrome. The patient gave a recent history of socio-familial stress. The patient was admitted in the internal ward as tetany. Two-calcium gluconate ampoules 10 ml 10% over IV over 20 minutes were taken. Complete clinical and electrocardiographic recovery (Figure 5).

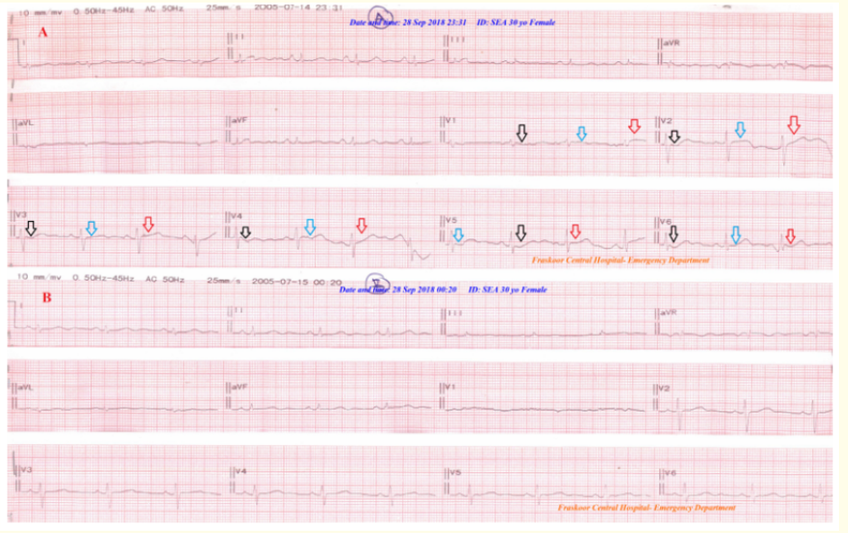

Figure 5: *A-ECG tracing of the ED presentation showing "Wavy triple sign" in V1-4 Leads. (red arrows = elevated beats, blue arrows = isoelectric beats, and black arrows = depressed beats). B-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 5: A 42-year-old married Egyptian housewife female patient presented to the POC with carpopedal spasm and psychogenic hyperventilation syndrome. The patient gave a recent history of socio-familial stress. The patient was admitted in the internal ward as tetany. One-calcium gluconate ampoule 10 ml 10% over IV over 10 minutes was taken. Complete clinical and electrocardiographic recovery (Figure 6).

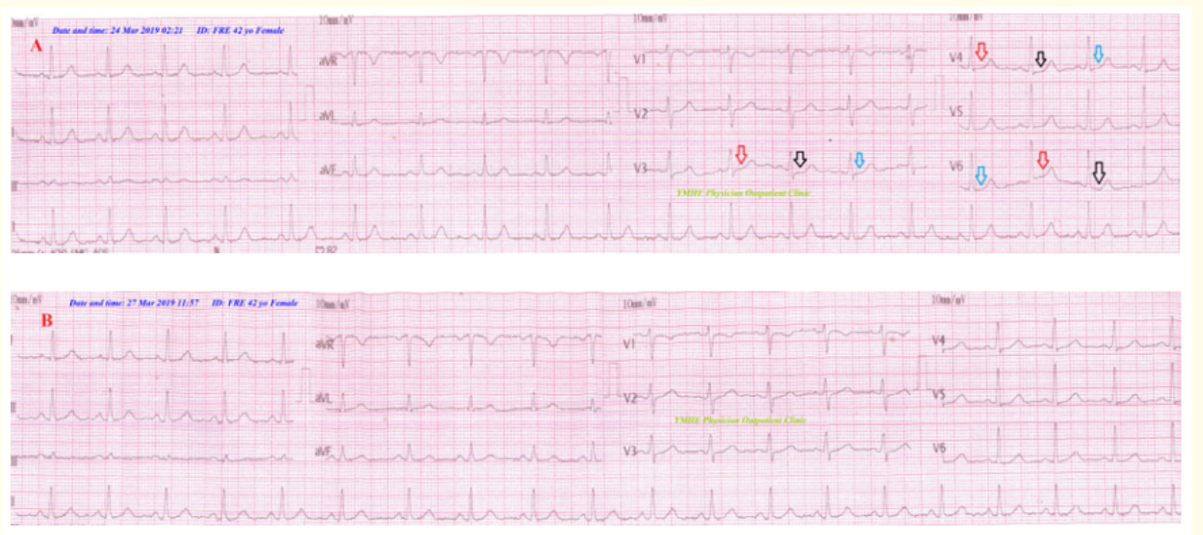

Figure 6: *A-ECG tracing of the POC presentation showing "Wavy triple sign" in V3,4 6 Leads. (red arrows = elevated beats, blue arrows = isoelectric beats, and black arrows = depressed beats). B-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 6: A 65-year-old married Egyptian male worker patient presented to the ED with spasm in all left upper limb, carpopedal spasm and uncontrolled hyperglycemia (RBS;532 with no ketosis). The patient gave a history of diabetes and liver cirrhosis. Upon examination; signs of chronic liver disease and right upper limb tetany were seen. The patient was admitted in the IW for both tetany and hyperglycemia. One-calcium gluconate ampoule 10 ml 10% over IV over 10 minutes was taken. Complete clinical and but partial electrocardiographic recovery (Figure 7). Management of diabetes in the chronic liver disease was given according to standard guideline.

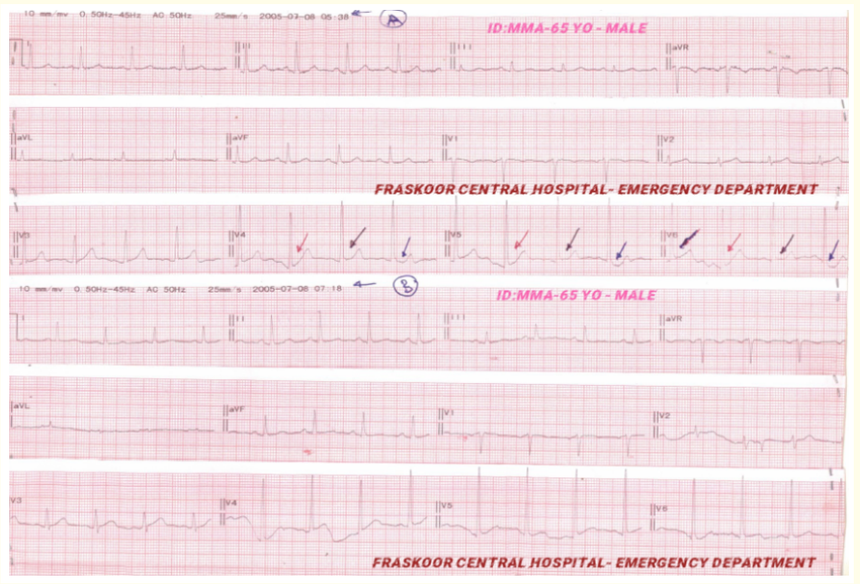

Figure 7: *A-ECG tracing of the POC presentation showing "Wavy triple sign" in V4-6 Leads. (red arrows = elevated beats, blue arrows = isoelectric beats, and black arrows = depressed beats). B-ECG tracing after calcium injection showing partial the disappearance of the previous sign.*

Case No. 7: A 30-year-old married Egyptian housewife female patient presented to the ED with carpopedal spasm and psychogenic hyperventilation syndrome. The patient gave a recent history of socio-familial stress. The patient was admitted in the ICU as tetany with chest pain. Two-calcium gluconate ampoules 10 ml 10% over IV over 20 minutes were taken. Complete clinical and electrocardiographic recovery (Figure 8).

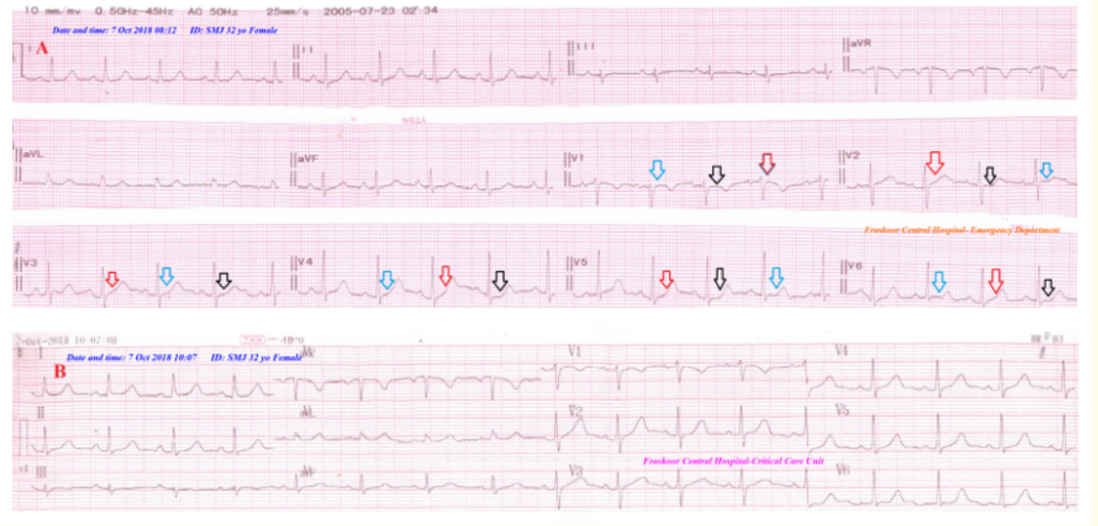

Figure 8: *A-ECG tracing of the ED presentation showing "Wavy triple sign" in V1-6 Leads. (red arrows =elevated beats, blue arrows = isoelectric beats, and black arrows = depressed beats). B-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 8: A 58-year-old married Egyptian male carpenter patient presented to the ED with carpopedal spasm. The patient gave a history of liver cirrhosis, hepatocellular carcinoma (HCC) and malnutrition. The patient was admitted in the IW for both tetany and chronic liver disease. One-calcium gluconate ampoule 10 ml 10% over IV over 10 minutes was taken. Complete clinical and electrocardiographic recovery (Figure 9). Management of chronic liver disease was given according to standard guideline.

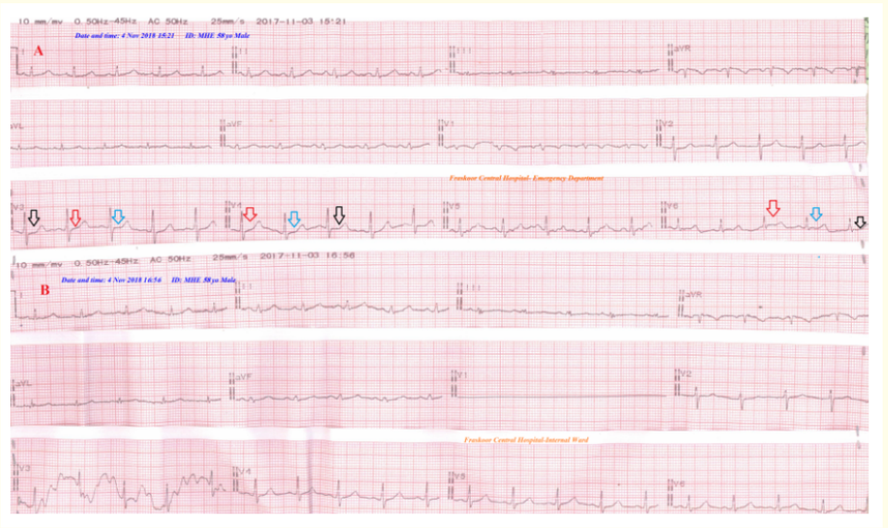

Figure 9: *A-ECG tracing of the ED presentation showing "Wavy triple sign" in V3,4,6 Leads. (red arrows = elevated beats, blue arrows = isoelectric beats, and black arrows = depressed beats). B-ECG tracing after calcium injection showing the disappearance of the previous sign in V4,6 But there is an artifact in V3, So, the author can't decide the effect.*

Case No. 9: A 75-year-old married Egyptian female housewife patient was admitted in the ICU with the cerebrovascular accident with infarction, hypertension and hyperventilation. One-calcium gluconate ampoule 10 ml 10% over IV over10 minutes was taken. Electrolytes profile and ABG were checked during hyperventilation episodes. Daily checked of calcium level throughout the hospital admission was recommended. Complete resolution of the electrocardiographic changes had happened (Figure 10).

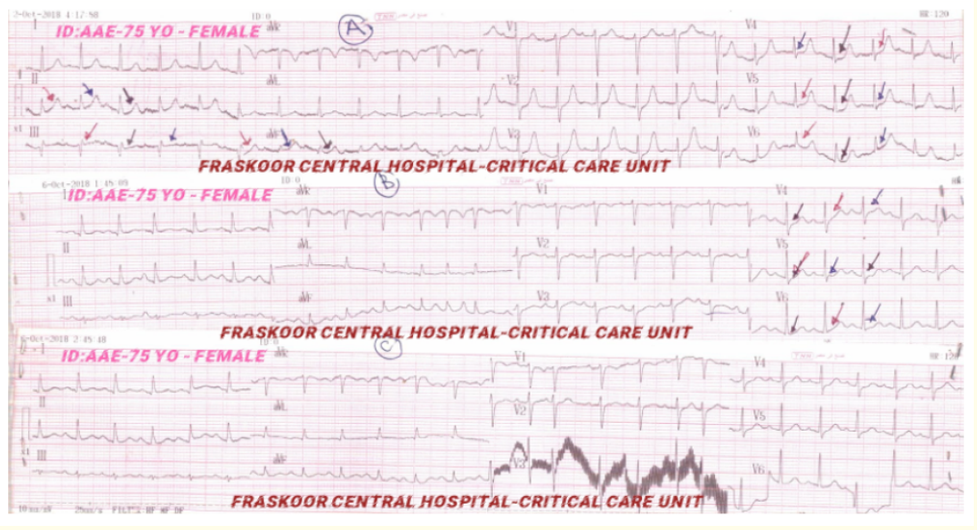

Figure 10: *A and B-ECG tracing during hyperventilation episodes showing "Wavy triple sign" in Leads: II, III, aVF and V4-6. (Red arrows =elevated beats, blue arrows = isoelectric beats, black arrows = depressed beats). C-ECG tracing after calcium injection showing the disappearance of the previous sign.*

Case No. 10: A 29-year-old married housewife Egyptian female patient presented to the POC with, perioral parathesia, extremities tingling, non-specific chest pain and fatigue. The patient gave a recent history of poor nutritional status due to heavy work. Trousseau and Chvostek's signs sign were elicited. The patient was managed with oral calcium capsule (600 mg, single daily dose). The ECG was done within 3 days of given oral calcium. Complete resolution of both clinical and electrocardiographic changes had happened (Figure 11).

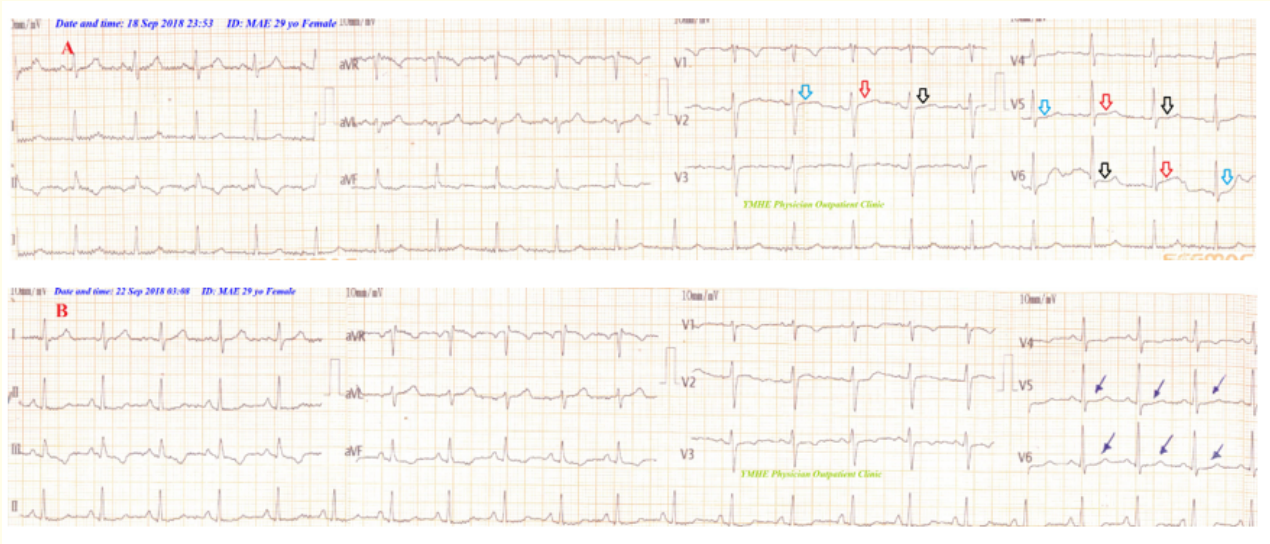

Figure 11: *A-ECG tracing of the presentation showing "Wavy triple sign" in Leads: V2,5,6. (Red arrows = elevated beats, blue arrows = isoelectric beats, black arrows = depressed beats). B-ECG tracing 3 days after of oral calcium showing the disappearance of the previous sign.*

Case No. 11: A 20-year-old single Egyptian student female patient presented to the ED with carpopedal spasm and psychogenic hyperventilation syndrome. The patient gave a recent history of psychological stress. The patient was admitted in the IW as tetany. The only ECG; V1,2 leads were involved. One-calcium gluconate ampoules 10 ml 10% over IV over 10 minutes was taken. Complete clinical and electrocardiographic recovery.

Case No. 12: A 50-year-old married Egyptian housewife female patient presented to the ED with carpopedal spasm and psychogenic hyperventilation syndrome. The patient gave a recent history of socio-familial stress. The patient was admitted in the IW as tetany. The only ECG; aVF, V2-6 leads were involved. Two-calcium gluconate ampoules 10 ml 10% over IV over 10 minutes were taken. Complete clinical and electrocardiographic recovery.

Case No. 13: A 13-year-old single Egyptian student female patient presented to the POC with carpopedal spasm and idiopathic hyperventilation syndrome. The patient was admitted in the ICU as tetany with chest pain. The only ECG; II, aVF,V1-6 leads were involved. This case is exceptional for the study. "Wavy triple sign" is replaced with: "Wavy double sign". So, there are only two affected beats; but not the three one like-Wavy triple sign. Two-calcium gluconate ampoules 10 ml 10% over IV over 20 minutes were taken. Complete clinical and electrocardiographic recovery (Figure 12).

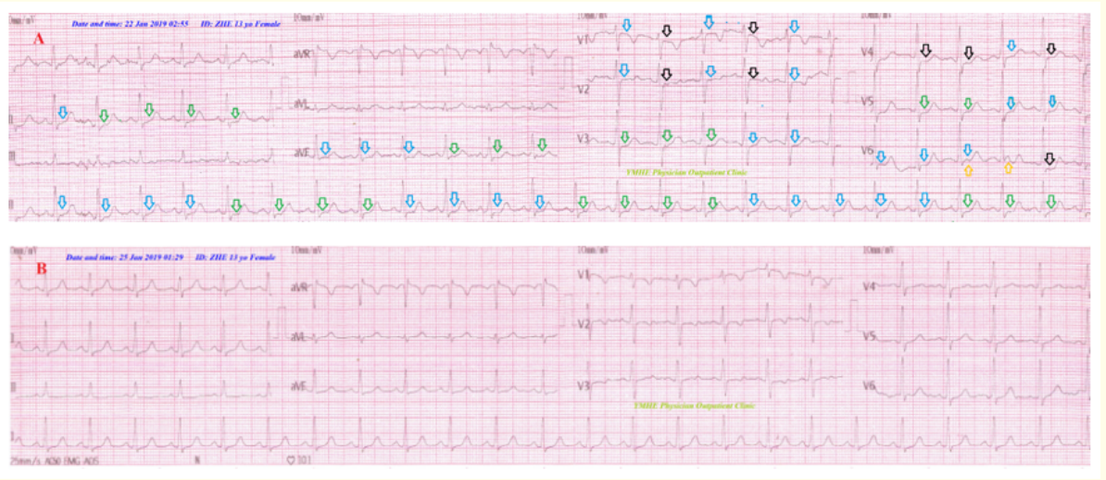

Figure 12: *A-ECG tracing of the presentation showing "Wavy triple sign" in Leads: II, aVF, V1-6. (Red arrows = elevated beats, blue arrows = isoelectric beats, black arrows = depressed beats). B-ECG tracing 3 days after calcium injection showing the disappearance of the previous sign.*

Case No. 14: A 39-year-old married Egyptian officer female patient presented to the ED with carpopedal spasm and idiopathic hyperventilation syndrome. The patient was admitted in the IW as tetany. The only ECG; I, II, aVF, V2 Leads were involved. One-calcium gluconate ampoules 10 ml 10% over IV over 10 minutes were taken. Complete clinical and electrocardiographic recovery.

Case No. 15: A 53-year-old married Egyptian housewife female patient presented to the ED with carpopedal spasm and hyperventilation syndrome. The patient gave a recent history of socio-familial stress. The patient was admitted in the ID as tetany. The only ECG; I, II, V2,4,5 leads were involved. Two-calcium gluconate ampoules 10 ml 10% over IV over 20 minutes were taken. Complete clinical and electrocardiographic recovery.

Results and Findings

Age averages in the study: Mean: 38.4, Median: 33, Mode: 30.

Sex in both groups: Female (F) 72.97% (27 cases) vs. Male (M) 27.03% (10 cases)

The main complaints in the study were: Carpopedal spasm (89.19%) vs. Parathesia and tingling (8.11%) and hyperventilation syndrome (2.7%) (Figure 13).

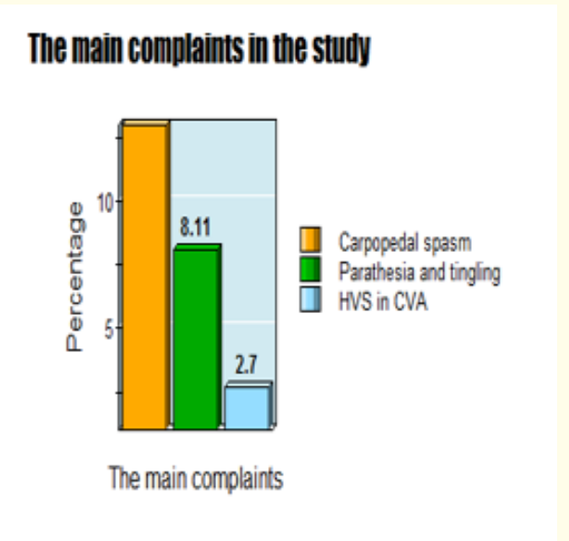

Figure 13: *Showing the main complaints in the study.*

The associated risk factors (RF) and etiology in the study:

- **HVS:** 45.95% (17 cases)
- **Malnutrition:** 24.32% (9 cases)

Combined RF:

- **Malnutrition + CLD:** 5.41% (2 cases)
- **Malnutrition + Elderly:** 2.7% (1 case)
- **HVS+ DKA:** 2.7% (1 case)
- **HVS+ Coffee:** 5.41% (2 cases)
- **HVS+ CVA:** 2.7% (1 case)
- **HVS+ Pregnancy:** 5.41% (2 cases)
- **HVS+ Marijuana:** 2.7% (1 case)
- **DKA+ CLD:** 2.7% (1 case) (Figure 14).

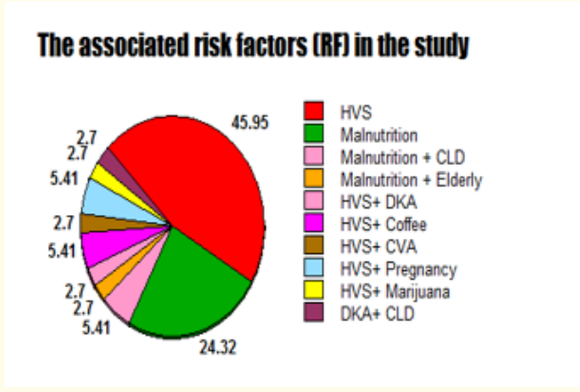

Figure 14: *Showing the associated risk factors (RF) and etiology in the study.*

The final diagnosis:

- **Manifested tetany:** 89.19% (33 cases)
- **Latent tetany:** 8.11% (3 cases)
- **Non-classifi**ed (During cerebrovascular accident): 2.7% (1 case) (Figure 15).

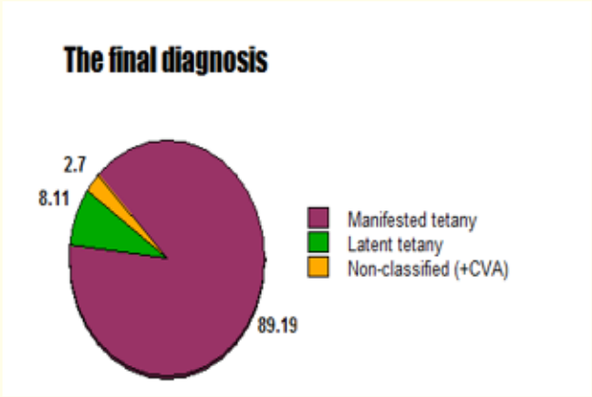

Figure 15: *Showing the final diagnosis for hypocalcemia in the study.*

The wavy triple sign is a positive and triple sign in 97.3% (36 cases) but it is only wavy double in 2.7% (case No. 13). So, the percent of the sign in the study in both group: 97.3% wavy triple (36 cases) vs. 2.7% of wavy double (one case; case No. 13).

Averages number of affected ECG leads (No. of leads); Mean: 4.13, Median: 3, Mode: 3, Max: 10, Min: 1.

The frequency for the number of affected ECG leads in the study (Figure 16).

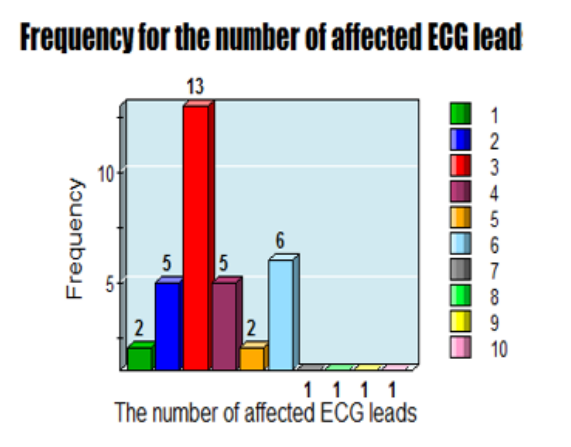

Figure 16: *Showing the frequency for the number of affected ECG leads in the study.*

The number of affected ECG leads vs. Level of ionized Ca^{++} in the first group (Figure 17).

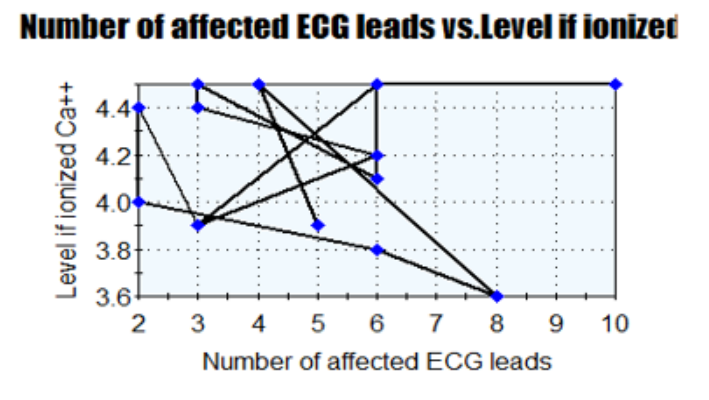

Figure 17: *Showing the number of affected ECG leads vs. the level of ionized Ca++ in the first group.*

ECG recovery after Ca^{++} administration in the first group (complete/partial): 97.3% complete vs. 2.7% partial ECG recovery (case No. 6).

Discussion

The principles of "Wavy triple an electrocardiographic sign (Yasser sign) in hypocalcemia" and their interpretations are depending on the following:

- Different subsequent three beats in the same lead are involved.
- Different leads may be affected.
- Mostly, there is no sharing part among the involved leads. The author intended that is not conditionally included especial coronary artery for the affected leads.
- An associated elevated beat is seen with the first of the subsequent three beats, depressed beat with the second beat and isoelectric ST segment in the third one.
- The elevated beat either associated with ST-segment elevation or just elevated beat above the isoelectric line. Also, the depressed beat either associated with ST-segment depression or just depressed beat below the isoelectric line.
- The arrangement for depressions, elevations and isoelectricities of ST-segment for the subsequent three beats are variable from case to case. So, this arrangement non-conditional.
- The wavy curve for the subsequent three beats from depressions, elevations and isoelectricities are noticed and prescribed (Figure 1).
- The wavy movements in myocardium or coronaries during tetany have suggested an explanation. These need further investigations.
- Variable but segmental ECG leads are involved.
- The extent and severity of ECG changes are related to serum calcium level in the investigated group.
- Tetany and latent hypocalcemia are included. Manifested tetany was the commonest final diagnosis (89.19%).
- Hyperventilation syndrome (45.95%) and malnutrition (24.32%) are the most common risk factors.
- Carpopedal spasm was the main complaint (89.19%).
- The Mean number of affected electrocardiographic leads: 4.13, Max.:10 and Min.:1).
- Dramatic improvement of both clinical manifestation and the new electrocardiographic sign simultaneously after calcium replacement had happened.
- Parenteral or oral calcium preparation was supplied.
- "Wavy triple an electrocardiographic sign" is a novel sign in hypocalcemia not recorded before.
- "Wavy triple an electrocardiographic sign" is a novel specific diagnostic ECG sign for hypocalcemia if compared with the old traditional non-specific ECG signs.
- "Wavy triple sign" is a positive and triple sign in 97.3% (36 cases) but it is only double in 2.7% (1 case).
- "Wavy triple an electrocardiographic sign" can be used as a therapeutic guide in the cases of hypocalcemia.
- Coronary artery spasm (CAS) is a possible differential diagnosis. But, in CAS; all beats of affected lead either regular depressed ST-segments or regular elevated ST-segments.

Conclusion

- "Wavy triple an electrocardiographic sign (Yasser sign)" is a new specific diagnostic sign seen in 97.3% of the cases of hypocalcemia. "Wavy triple an electrocardiographic sign" can be used as a therapeutic guide in the cases of hypocalcemia.
- Further investigations for the "Wavy triple an electrocardiographic sign (Yasser sign)" for more evaluation and assessment are recommended.

Conflicts of Interest

There are no conflicts of interest.

Acknowledgment

I wish to thank Dr. Ameer Mekkawy; M.Sc. for technical support and nurses of the Critical Care Unit and Emergency Department who make extra ECG copy for helping me.

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Volume 3 Issue 12 December 2019