Brugada Phenocopy in methanol toxicity: A novel marker of mortality

Mohammad Hossein Nikoo[1], Alireza Estedal[2], Kiana Khatami[2], Maryam Pakfetrat[3], Alireza Arjangzadeh[4], Shahrokh Sadeghi Boogar[3], Sina Danesh[2], Seyed Taghi Heydari[2]

[1]Non-communicable Disease Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Fars, Iran.

[3]Department of Internal Medicine, Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[4]Cardiology Department, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding author

Seyed Taghi Heydari

Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Fars, Iran. Email: heydari.st@gmail.com.

Tel: +989173034420. Fax: +98-711-2309615

Address: Health Policy Research Center, Building No.2.8th Floor School of Medicine Zand Avenue, Shiraz, Iran, P.O.Box:71345-1877.

Abstract

Introduction: Brugada phenocopies are recently introduced as clinical entities with electrocardiographic patterns identical to true congenital Brugada syndrome in individuals, who are asymptomatic and have no other clinical criteria. One of the largest methanol poisoning outbreaks occurred in Iran during March and April 2020. This study aimed to investigate the relationship between Brugada Phenocopy with laboratory data and demographic factors and determine its association with mortality rate in methanol toxicity patients.

Method and results: Demographic data such as age, gender, medical history, Glasgow coma scale score, laboratory data, and electrocardiographic data were obtained from 356 patients, who were diagnosed with methanol poisoning and were hospitalized in Faghihi and Namazi Hospitals in Shiraz, southern Iran, during March and April 2020. The follow-up data was gathered to examine the development of any complications or death. A total of 20 (5.6%) patients were admitted with a diagnosis of methanol toxicity and concurrent Brugada-like ECG patterns. Mortality rate, Glasgow Coma Scale Score <3, and blood sugar were significantly higher in the Brugada phenocopies; however, PH, O2 saturation, and calcium were lower among Brugada phenocopies in comparison to methanol toxicity patients with no Brugada pattern ($P<0.05$).

Conclusion: According to the findings of this study, some recognizable ECG patterns and laboratory data may be used as novel prognostic factors of morbidity and mortality. Electrocardiography machines are widely available, and electrocardiograms can easily be obtained and interpreted. This may provide the grounds for caregivers to predict and prevent the incoming death and react more properly and timely.

Keywords: Brugada Phenocopy, Mortality, Methanol poisoning, Iran

1. Introduction

The Brugada syndrome (BrS) is an autosomal dominant genetic disorder with variable expressions characterized by abnormal findings on the surface electrocardiogram (ECG) regarding an increased risk of ventricular tachyarrhythmias and sudden cardiac deaths.[1] Brugada phenocopies (BrP) are recently introduced as clinical entities with electrocardiographic patterns identical to true congenital Brugada syndrome in individuals, who are asymptomatic and have no other clinical criteria.[2,3] These Brugada-like ECG patterns are presented under various clinical conditions such as myocardial ischemia and diseases, mechanical chest compression, pulmonary embolism, electrolyte imbalances, and metabolic derangements and are provoked by the administration of special medications.[2,4-7]

Methanol (also known as methyl alcohol, wood alcohol, wood spirits, and carbinol) is a widely available chemical in industries and a number of household products, including varnish, windscreen washer fluid, and antifreezes. Methanol has a relatively low intrinsic toxicity; however, it is metabolized in human body and converts into highly toxic compounds such as formaldehyde, formic acid, and formate, which can cause blindness, coma, and life-threatening metabolic disturbances.[8,9] Owing to the long-term effects of these toxic metabolites, victims do not often detected at an appropriate time; hence, the delayed treatment of such patients contributes to the high rates of morbidity and mortality in the outbreaks of methanol poisoning. Due to erroneous techniques in the production of alcoholic beverages, methanol toxicity outbreaks occur more frequently in some developing countries.[10]

During March and April 2020 in Iran, a major methanol outbreak occurred in the wake of the of COVID-19 pandemic, resulting in an extensive death toll of about 534 persons.[11] Considering the

major health burden imposed by the harmful use of alcohol, this study further investigated the risk factors associated with methanol toxicity. Brugada Phenocopy is one of the most interesting one, which has been explained recently. Reviewing the literature, Monterrubio-Villar[12] in his case report presented a 54-year-old man with the extreme metabolic acidosis and a Brugada type 1 ECG pattern, which later led to the patient's brain death. Moreover, Jaff et al.[13] reported a type 1 Brugada ECG pattern in a patient concurrently sedated with an infusion of propofol, who later developed permanent neurologic damage and expired. This study sheds more lights on the Brugada Phenocopy by describing a detailed examination of 20 patients presented with Brugada ECG pattern and is to highlight the significance of this finding as a mortality marker.

2. Methods

Data were collected from 356 patients, who were diagnosed with methanol poisoning and were hospitalized in Faghihi and Namazi Hospitals in Shiraz, southern Iran, during March and April 2020. These two tertiary-care hospitals are affiliated to Shiraz University of Medical Sciences and are the largest referral centers for all specialties and sub-specialties in Shiraz. Some poisoning care referral centers were specified at these hospitals during this outbreak. Demographic data such as age, gender, medical history, Glasgow coma scale score, development of any complications such as decreased visual acuity or renal problems, and mortality or survival during hospitalization course were obtained by the physician from the admission sheets. Laboratory data such as arterial blood gas data (pH, partial pressure of carbon dioxide (torr), bicarbonate (meq/L)), oxygen saturation (%), creatinine level (mg/dL), blood urine nitrogen level (mg/dL), blood sugar (mg/dL), and electrolyte variables, including sodium (meq/L), potassium

(meq/L), magnesium (mg/dL), and calcium (mg/dL), were gathered using the HIS (Health Information System) of the affiliated hospitals.

Brugada Phenocopy was diagnosed by identifying the characteristic patterns of Brugada syndrome on a standard 12- lead electrocardiogram in the absence of a true congenital Brugada syndrome. Three forms of the Brugada ECG pattern are described: Type 1 pattern has j point elevation, "coved-type" ST segment, and an inverted T wave in V1 and V2. Type 2 pattern has a "saddleback" ST-segment with at least 1 mm elevation, and Type 3 pattern has either type or type 2 pattern with less than 2 mm J-point elevation and less than 1 mm ST elevation. Cardiax PC ECG was used to obtain the electrocardiographic data, and the data was collected by a cardiologist. These ECGs were analyzed and reported independently by two cardiologists.

2.1 Statistical analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) Version 21.0 was used to analyze the data. Frequency (%) was used for the categorical variables such as gender, alcohol dependency, comorbidity, and Brugada Phenocopy. Moreover, mean ± standard deviation was used for age and laboratory findings. Independent sample t-test was used to compare the mean of the laboratory findings (namely PH, Hco3, Pco2, BUN, Cr, etc.) and Brugada Phenocopy. Chi-squared test was used to assess the relationships between Brugada Phenocopy and previous cardiac and non-cardiac diseases, death, renal failure, and decreased visual acuity. $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 20 (5.6%) patients were admitted with the diagnosis of methanol toxicity and concurrent Brugada-like ECG patterns, among whom four (20.0%) patients had Type 1, three (15.0%) patients had type 2, and 13 (65.0%) patients had type 3 Brugada phenocopies. Interestingly, none of these patients had a history of medical diseases. Comparing Brugada Phenocopy patients with normal methanol toxicity patients revealed that mortality rate (Brugada: 45.0%, non-Brugada: 13.5%, $p<0.001$), renal failure (Brugada: 65.0%, non-Brugada: 34.3%, $P=0.008$), Glasgow Coma Scale Score < 3 (Brugada: 35.0%, non-Brugada: 11.5%, $P=0.008$), and blood sugar (Brugada: 227.25±124.15, non-Brugada: 139.17±92.23, $P<0.001$) were significantly higher in the former group. In addition, PH (Brugada: 7.01±0.26, non-Brugada: 7.15±0.21, $P=0.006$), O2 saturation (Brugada: 81.94±13.70, non-Brugada: 91.04±9.90, $P<0.001$) and calcium (Brugada: 10.05±1.34, non-Brugada: 9.53±0.725, $P=0.018$) were lower in Brugada phenocopy patients, compared to methanol toxicity patients with no Brugada ECG pattern (Table 1). No significant difference was observed between the two groups in terms of age, gender, medical history, decreased visual acuity, Bicarbonate, partial pressure of CO2, creatinine, sodium, potassium, and magnesium.

In patients with type 1 Brugada Phenocopy, Potassium (7.05±1.20, P=0.001) and blood sugar (278.75±46.70, P=0.001) were higher, and oxygen saturation (69.75±9.95, P<0.001), PH (6.76±0.083, P=0.002) and calcium levels (9.50±0.36, P=0.048) were lower in comparison to the other Brugada pattern types. Furthermore, no significant difference was detected between the two groups in terms of age, Bicarbonate, partial pressure of CO2, Blood urine nitrogen, sodium, potassium, and magnesium (Table 2).

4. Discussion

Brugada syndrome has originally been described as a distinct clinical and electrocardiographic syndrome characterized by ST elevation with successive negative T wave in the right precordial leads, predisposing patients to the risk of sudden cardiac death (SCD) due to ventricular fibrillation (VF).[14] In this regard, a number of Brugada-like ECG patterns have been observed under various underlying clinical conditions, leading to the proposal of "Brugada Phenocopy" by Riera et al.[6] and the further characterization of this clinical entity.[15]. However, Brugada syndrome and Brugada-like ECG patterns have been the subject of a number of controversies regarding the casual role of genetic variants and their underlying pathophysiology.

According to the present findings, the higher levels of acidosis was significantly associated with the presentation of Brugada-like ECG patterns. These values are mainly in line with the previous studies and further support the idea that external PH affects sodium channel function, resulting in acidosis-induced arrhythmias and triggering Brugada syndrome and sudden cardiac deaths.[16-20] In addition, the first putative mutations leading to Brugada syndrome were found in SCN5A, which encodes the cardiac sodium channel NaV1.5.[21] The fact that the function of this subunit is attenuated by acidosis also gave rise to our hypothesis indicating that low PH can play a major role in Brugada Phenocopy as well as Brugada syndrome.

Another finding was the higher proportion of patients with decreased level of consciousness among Brugada phenocopies, in comparison to the other patients. This is in line with the findings of similar case report on methanol poisoning.[12] A review of the literature indicated that Brugada syndrome can be provoked in conditions with decreased brain function such as during sleep[22] and brain injury [23] and among patients with prolonged intubation in Intensive Care Units (ICU), sedative drugs overdoses[24-26] and propofol anesthesia.[6] This finding posed further questions

regarding the association between decreased levels of consciousness and lower brain function with the presence of Brugada-like ECG patterns.

Moreover, it was observed that Brugada Phenocopy patients had lower levels of serum calcium. The same is reported in previous studies. This may be due to the fact that the mutated sodium channel impairs the function of sodium-calcium exchanger, thus leading to such alteration.[27]

Another noticeable finding was that, among the three types of Brugada ECG patterns, Type 1 ECG pattern was presented with more dramatic laboratory alterations, in comparison to the other ECG types. More severe acidosis, higher potassium and blood sugar levels and lower calcium levels were observed in Type 1 Bdugada-like ECG patterns. This finding makes future researchers detect the association between laboratory data alterations and the severity of ECG changes.

4.1 Limitations

To the best of our knowledge, this is the first study focusing on Brugada Phenocopy in details. As predicted, there were some discrepancies about this topic due to the controversies and limited published data; hence, this was difficult to explain the exact underlying mechanisms.

4.2 Conclusion

Introducing a recognizable ECG pattern may provide the grounds for caregivers to predict and prevent the incoming death and react more properly and timely. Given the availability of ECG machine and the ease of taking the ECG and its rapid interpretation, we hope more lives to be saved using this marker by toxicologists. The correction of acidosis, hypocalcemia, and

hypokalemia can be a technique to reduce the pattern; however, there is a need for further research.

Acknowledgements

The present study was supported the Vice-chancellor for Research, Shiraz University of Medical Sciences, Shiraz, Iran. The authors would also like to show our great appreciation for help by Mohammadali Nikoo in scientific writing.

Funding

The research grant provided by Research Deputy of Shiraz University of Medical Sciences (number: 98–01–01-22074). Funding body of the study did not play any role in the design of the study, collection, analysis, and interpretation of data and in writing the manuscript.

Ethics approval

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.059).

Conflicts of interests

The authors declare that they have no conflict of interest.

References

1. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. *Journal of the American College of Cardiology*. 2018;72(9):1046-1059.
2. Anselm DD, Evans JM, Baranchuk A. Brugada phenocopy: A new electrocardiogram phenomenon. *World journal of cardiology*. 2014;6(3):81-86.
3. Dendramis G. Brugada syndrome and Brugada phenocopy. The importance of a differential diagnosis. In: Elsevier; 2016.
4. Anselm DD, Gottschalk BH, Baranchuk A. Brugada phenocopies: consideration of morphologic criteria and early findings from an international registry. *Canadian Journal of Cardiology*. 2014;30(12):1511-1515.
5. Anselm DD, Baranchuk A. Brugada Phenocopy in the context of pulmonary embolism. *International journal of cardiology*. 2013;168(1):560.
6. Riera ARP, Uchida AH, Schapachnik E, Dubner S, Ferreira Filho C, Ferreira C. Propofol infusion syndrome and Brugada syndrome electrocardiographic phenocopy. *Cardiology journal*. 2010;17(2):130-135.
7. Kovacic JC, Kuchar DL. Brugada pattern electrocardiographic changes associated with profound electrolyte disturbance. *Pacing and clinical electrophysiology*. 2004;27(7):1020-1023.
8. Poisoning AAoCTAHCotTGfM, Barceloux DG, Randall Bond G, Krenzelok EP, Cooper H, Allister Vale J. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *Journal of Toxicology: Clinical Toxicology*. 2002;40(4):415-446.
9. Liesivuori J, Savolainen, Heikki. Methanol and formic acid toxicity: biochemical mechanisms. *Pharmacology & toxicology*. 1991;69(3):157-163.
10. Beauchamp GA, Valento M. Toxic Alcohol Ingestion: Prompt Recognition And Management In The Emergency Department. *Emergency medicine practice*. 2016;18(9):1-20.
11. Hassanian-Moghaddam H, Zamani N, Kolahi AA, McDonald R, Hovda KE. Double trouble: methanol outbreak in the wake of the COVID-19 pandemic in Iran-a cross-sectional assessment. *Critical care (London, England)*. 2020;24(1):402.
12. Monterrubio-Villar J, Llinares-Moya D. Brugada Phenocopy Induced by a Lethal Methanol Intoxication. *European journal of case reports in internal medicine*. 2020;7(2):001374.
13. Jaff Z, McIntyre WF, Yazdan-Ashoori P, Baranchuk A. Impact of methanol intoxication on the human electrocardiogram. *Cardiology journal*. 2014;21(2):170-175.
14. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *Journal of the American College of Cardiology*. 1992;20(6):1391-1396.
15. Anselm DD, Baranchuk A. Brugada phenocopy: redefinition and updated classification. *American Journal of Cardiology*. 2013;111(3):453.
16. Vilin YY, Peters CH, Ruben P. Acidosis differentially modulates inactivation in Nav1. 2, Nav1. 4, and Nav1. 5 channels. *Frontiers in pharmacology*. 2012;3:109.
17. Wagner EM, Brumback BD, Voelker TL, Zhu W, Silva JR. Extracellular Acidosis Exhibits Domain-Specific Effects on Nav1. 5. *Biophysical Journal*. 2019;116(3):390a.
18. Sokolov S, Peters CH, Rajamani S, Ruben PC. Proton-dependent inhibition of the cardiac sodium channel Nav1. 5 by ranolazine. *Frontiers in pharmacology*. 2013;4:78.
19. Peters CH, Ruben PC. Acidosis: A Possible Trigger for Brugada Syndrome Associated Arrhythmia. *Biophysical Journal*. 2014;106(2):327a.
20. Jones DK, Peters CH, Tolhurst SA, Claydon TW, Ruben PC. Extracellular Proton Modulation of the Cardiac Voltage-Gated Sodium Channel, NaV1.5. *Biophysical Journal*. 2011;101(9):2147-2156.

21. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm*. 2010;7(1):33-46.
22. Antzelevitch C. The brugada syndrome. *Journal of cardiovascular electrophysiology*. 1998;9:513-516.
23. Derevjaník M, Šedivá L. Brugada syndrome – Case report, risk stratification and treatment. *Cor et Vasa*. 2016;58(5):e491-e496.
24. Monteban-Kooistra WE, van den Berg MP, Tulleken JE, Ligtenberg JJ, Meertens JH, Zijlstra JG. Brugada electrocardiographic pattern elicited by cyclic antidepressants overdose. *Intensive care medicine*. 2006;32(2):281-285.
25. Bigwood B, Galler D, Amir N, Smith W. Brugada syndrome following tricyclic antidepressant overdose. *Anaesthesia and intensive care*. 2005;33(2):266-270.
26. Levine M, LoVecchio F. Diphenhydramine-induced Brugada pattern. *Resuscitation*. 2010;81(4):503-504.
27. Monasky MM, Pappone C, Piccoli M, Ghiroldi A, Micaglio E, Anastasia L. Calcium in Brugada Syndrome: Questions for Future Research. *Frontiers in Physiology*. 2018;9(1088).