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Case Report

Brugada syndrome with a novel missense mutation in SCN5A gene: A case report from Bangladesh

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ABSTRACT

Brugada syndrome is an inherited cardiac arrhythmia that follows autosomal dominant transmission and can cause sudden death. We report a case of Brugada syndrome in a 55-year-old male patient presented with recurrent palpitation, atypical chest pain and pre-syncope. ECG changes were consistent with type 1 Brugada. Gene analysis revealed a novel missense mutation in SCN5A gene with a genetic variation of D785N and a nucleotide change at 2353G-A. One of his children also had the same mutation. To our knowledge this is the first genetically proved case of Brugada syndrome in Bangladesh.

1. Introduction

Brugada syndrome is an inherited cardiac arrhythmia that follows autosomal dominant mode of transmission. It can cause syncope and sudden cardiac death in young individuals with structurally normal heart due to rapid polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). Brugada ECG is typically characterized by down sloping ST segment elevation (coving type) in the right precordial leads.[1] These characteristics exhibit day-to-day variation and may not always be present.[2] Commonly the incidence of arrhythmia occurs during resting period and often during sleep.[3] It has long been recognized as SUDS (sudden unexplained death syndrome) in different regions of South-east Asia.[4]

Brugada syndrome is genetically heterogeneous and is linked to at least 8 different genes. Since its first diagnosis in 1992, a number of new genes linked to the disease and new mutations are being consistently found. The commonest mutation is in the SCN5A gene on chromosome 3, which encodes the pore-forming subunit of the cardiac voltage-gated sodium channel.[5] Although prevalent in Southeast Asia there has been no case reported from Bangladesh.

The present case report is first of its kind where a new and previously unpublished mutation in SCN5A gene was detected for Brugada syndrome.

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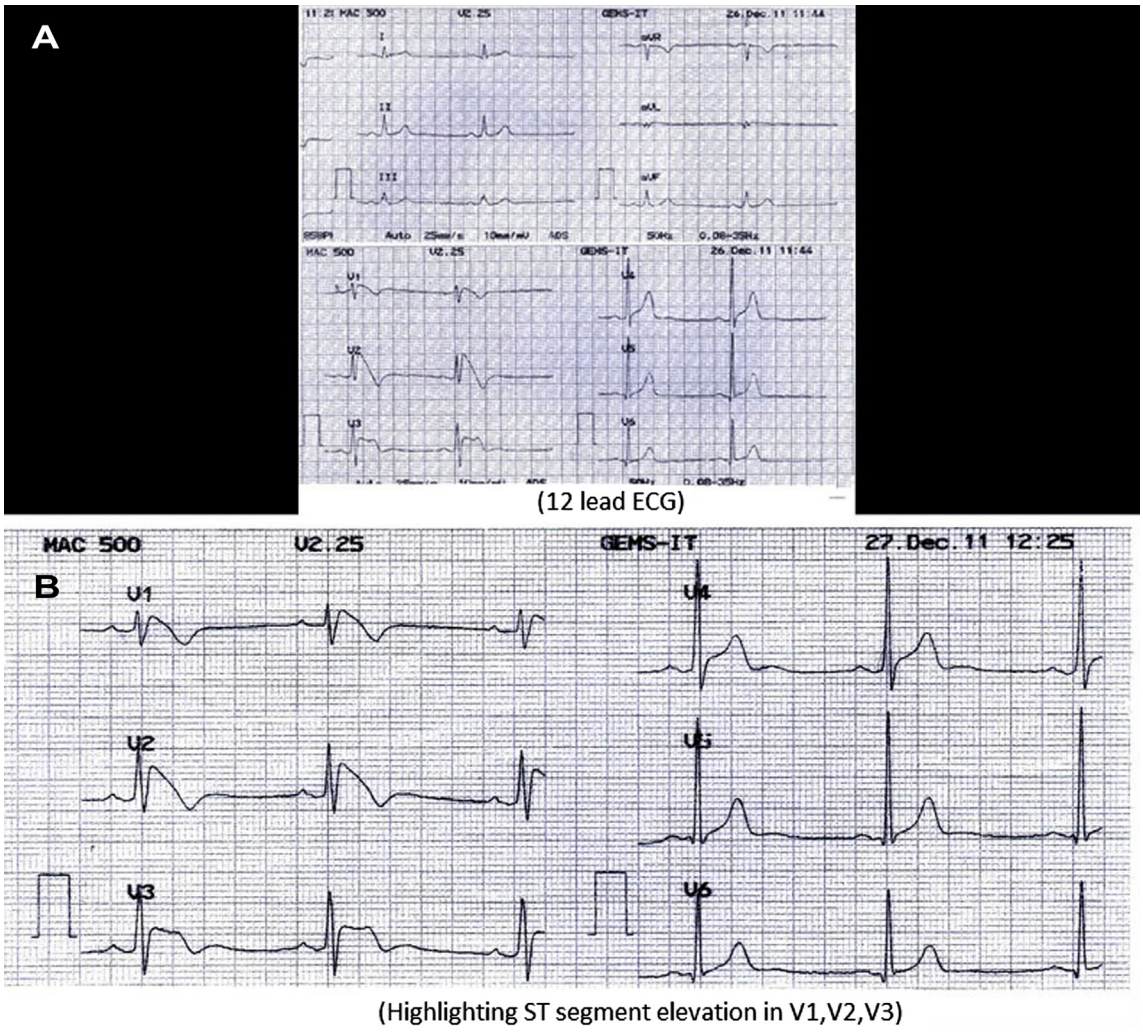

Fig. 1 – (A and B): 12 lead initial ECG taken on 26/11/2011 showing type 1 Brugada pattern (A) and highlighted ST segment elevation (coving type) in leads V_1, V_2 and V_3 taken on 27/11/2011 (B).

2. Case report

A 55-year-old male subsistence farmer was admitted in the Cardiology unit of Rajshahi Medical College Hospital with recurrent palpitation, atypical chest pain, dizzy feeling and occasional presyncope that aggravated during last 1 year especially on exposure to hot environment. He had no history of night terror or agonal respiration. His initial ECG showed down sloping ST segment elevation in V_1, V_2 and V_3 leads consistent with type 1 Brugada ECG (Fig. 1A and B). There is no history of sudden death in his family. His physical examination was unremarkable and serial ECGs remained the same. He was a heavy smoker but nondiabetic, normolipidaemic with normal electrolyte and cardiac enzyme level. His chest X-ray and echocardiogram were normal and coronary angiogram revealed normal coronaries. The patient was then provisionally diagnosed as suffering from Brugada syndrome. Genetic diagnosis was done at the Ramon Brugada Sr. foundation, Cardiovascular Genetics Centre of Girona, Spain, that revealed a novel missense mutation in SCN5A gene within exon 15 of chromosome 3 with a genetic variation of D785N and a nucleotide change at 2353G-A (Fig. 2). His eldest son aged 39 years was mildly symptomatic with type III Brugada ECG, had the same mutation, but no mutation was detected in daughter's sample.

Both father and the son were advised for regular follow up. Avoidance of precipitating drugs, hot environment, emotion, excitement and prompt use of antipyretic in fever was stressed. Considering symptoms, ECG changes and genetic test result ICD was indicated but patient could not afford it due to high cost involved.

3. Discussion

In 1992 Dr. Pedro and Joseph Brugada first described a new clinical entity causing life-threatening ventricular tachyarrhythmia in patients with structurally normal heart which later was named as Brugada syndrome.[1,6] Although the disease is prevalent in Southeast Asia[7] but to the best of our

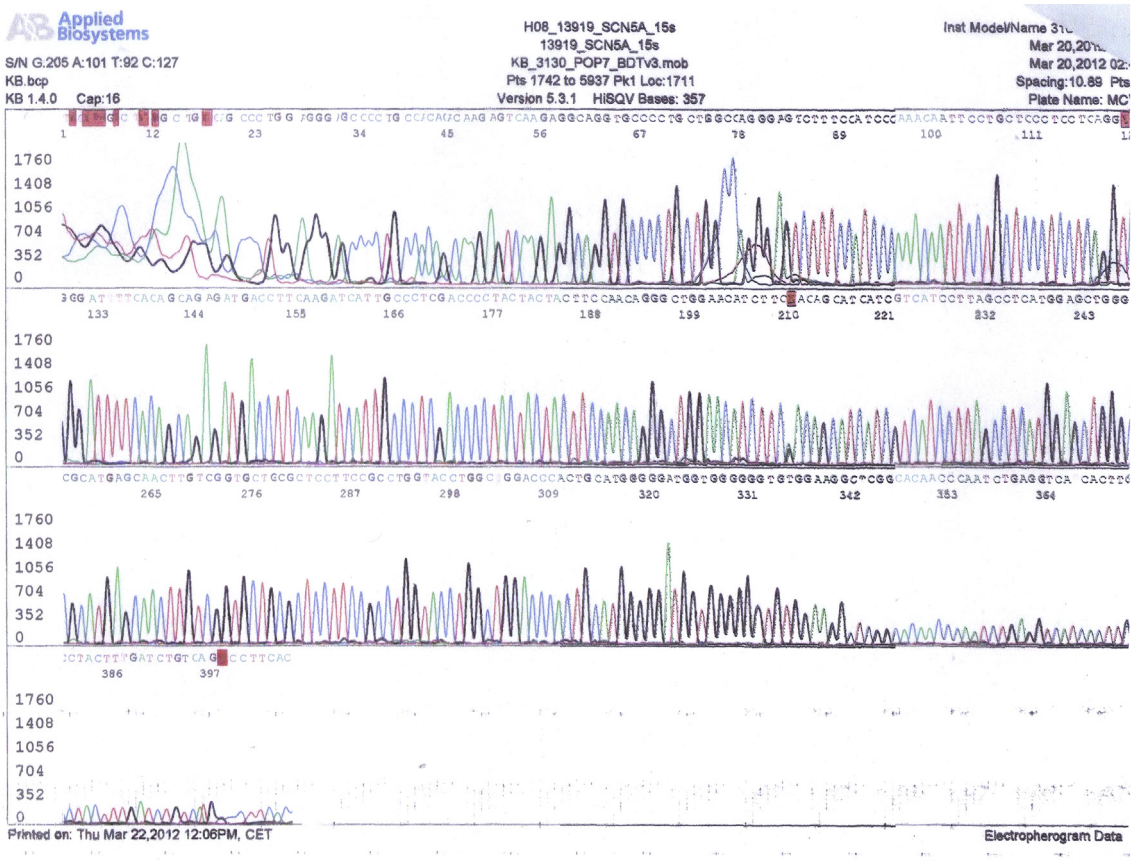

Fig. 2 – DNA sequencing showing mutation in SCN5A gene within exon 15 of chromosome 3 with a genetic variation of D785N and a nucleotide change at 2353G-A.

knowledge, there has been no such case reported from Bangladesh. Our clinical suspicion of Brugada syndrome was validated through genetic test from an authentic centre which confirmed a new mutation in SCN5A gene. The same new mutation was inherited by the proband's eldest son (only two of his five children agreed for gene testing) who was mildly symptomatic.

To rule out the polymorphism a large database (exome sequencing project) containing more than 10,000 alleles (American and European controls) (http://evs.gs.washington.edu/EVS/) was checked along with 1000 genome project (http://browser.1000genomes.org/index.html) but no such mutation was found in those controls. In Silico analysis (computational analysis programs that predict the pathogenesis of a variation) done in Girona, Spain, also ruled out the prediction of a polymorphism. Functional analysis of the mutation could be done, but it was not the usual protocol of that centre and other centres as well due to the length of the test. Expert opinion in this regard states that, if a variation has been found it is generally assumed to be pathogenic since controls worldwide do not have such variation. So by method of exclusion, eventually this was considered a new mutation of Brugada syndrome in our case.

Overall, 293 distinct possible BrS1-associated mutations in SCN5A have been linked to the symptom in recent years.[8] Until now there have been mutations in 8 genes including SCN5A that are known to cause Brugada syndrome.[9]

Considering the presence of new mutation in SCN5A gene in our case, it can be well said that this is a case of Brugada syndrome type 1. The proband has transmitted the mutation to one of his offspring's but lack of history of sudden death or typical clinical features among his close relatives lead to the sporadic nature of mutation in his case, although familial forms are more common.[10]

Our patient presented with a clear type 1 Brugada ECG that remained unchanged during follow up, so provocative test with Ajmaline or Flecainide (sodium channel blocker) was not considered. But it can be used as adjunct to substantiate the clinical diagnosis of Brugada type 2 or type 3 ECG and dynamic type 1 ECG.

In patients with Brugada syndrome and documented cardiac arrest, ICD implantation is mandatory. In the remaining patients, who constitute the vast majority of subjects encountered in the clinical setting, the best policy is unclear.[11] As our patient was symptomatic with type 1 Brugada ECG, confirmed by genetic testing, ICD was indicated but due to financial constraints of the patient it could not be given.

Further electrophysiology is usually done to substantiate the clinical diagnosis and for risk stratification in Brugada. We didn't go for electrophysiology as patient declined ICD.

Although genetic testing usually confirms mutation and new mutation in suspected cases but it is not widely available, costly and moreover it cannot help in risk stratification. Thus genetic testing is not routinely done for diagnosis of Brugada syndrome.

4. Conclusion

This is the first genetically proved case of Brugada syndrome reported from Bangladesh. But considering its prevalence in the neighboring countries, it is assumed that Brugada syndrome should have been prevalent here too. So diagnosis of Brugada syndrome should be kept in consideration in patients with suggestive symptoms or ECG changes.

Conflicts of interest

All authors have none to declare.

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REFERENCES

1. 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. *J Am Coll Cardiol*. 1992;20:1391–1396.
2. Veltmann C, Schimpf R, Echternach C, et al. A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification. *Eur Heart J*. 2006;27:2544–2552.
3. Matsuo K, Kurita T, Inagaki M, et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. *Eur Heart J*. 1999;20:465–470.
4. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol*. 2000;86:91–94.
5. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998;392:293–296.
6. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005;111:659–670.
7. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexpected death syndrome in Thai men. *Circulation*. 1997;96:2595–2600.
8. 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;7:33–46.
9. Brugada R, Campuzano O, Brugada P, et al. Brugada syndrome. GeneReviews™ [Internet]. 2012 (NCBI-NIH PMID20301690, Accessed on 19.01.13).
10. Schulze-Bahr E, Eckardt L, Breithardt G, et al. Sodium channel gene (SCN5A) mutations in 44 index patients with Brugada syndrome: different incidences in familial and sporadic disease. *Hum Mutat*. 2003;21:651–652.
11. Zipes DP, Camm JA, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhytmias and the prevention of sudden cardiac death. A report of the American College of Cardiology/American Heart Association Task Force and the Europe Society of Cardiology Committee for Practice Guidelines developed in collaboration with European Heart Rhythm Association and the Heart Rhythm Society. *Europace*. 2006;8:746–837.