Functional Bowel Disorders in Patients with Brugada Syndrome and Drug-Induced Type 1 Brugada Pattern

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Brief Title: Irritable Bowel Syndrome and Brugada Syndrome

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Structured Abstract

Introduction: Irritable bowel syndrome (IBS) is one of the most widely recognized functional bowel disorders (FBDs) with a genetic component. *SCN5A* gene and *SCN1B* loci have been identified in population-based IBS cohorts and proposed to have a mechanistic role in the pathophysiology of IBS. These same genes have been associated with Brugada syndrome (BrS). The present study examines the hypothesis that these two inherited syndromes are linked.

Methods and Results: Prevalence of FBDs over a 12 months period were compared between probands with BrS/drug-induced type 1 Brugada pattern (DI-Type 1 BrP) (n=148) and a control group (n=124) matched for age, female sex, presence of arrhythmia and co-morbid conditions. *SCN5A/SCN1B* genes were screened in 88 patients. Prevalence of IBS was 25% in patients with BrS/DI-Type 1 BrP and 8.1% in the control group ($p=2.34\times10^{-4}$). On stepwise logistic regression analysis, presence of current and/or history of migraine (OR of 2.75; 95% CI: 1.08 to 6.98; p=0.033) was a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. We identified 8 putative *SCN5A/SCN1B* variants in 7 (12.3%) patients with BrS/DI-Type 1 BrP and 1 (3.2%) patient in control group. Five out of 8 (62.5%) patients with *SCN5A/SCN1B* variants had FBDs.

Conclusion: IBS is a common co-morbidity in patients with BrS/DI-Type 1 BrP. Presence of current and/or history of migraine is a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. Frequent co-existence of IBS and BrS/DI-Type 1 BrP necessitates cautious use of certain drugs among the therapeutic options for IBS that are known to exacerbate the Brugada phenotype.

Key words: J Wave Syndromes, Functional Bowel Disorders, Irritable Bowel Syndrome, Epidemiology, Genetics

Introduction

Functional bowel disorders (FBDs) are a spectrum of chronic gastrointestinal disorders characterized by predominant symptoms and/or signs of abdominal pain, bloating, distention, and/or bowel habit abnormalities.[1] Irritable bowel syndrome (IBS) based on the Rome III diagnostic criteria is one of the most widely recognized FBDs, with more than 10% of the global adult population reporting symptoms compatible with the condition in population-based surveys.[2] To date, over a hundred genetic variants in over 60 genes from various pathways have been studied in a number of candidate gene studies with several positive associations reported. These findings suggest that there may be distinct, as well as shared molecular underpinnings for IBS.[3]

Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome characterized by a distinct ST-segment elevation in the right precordial leads in the absence of structural heart disease.[4] Type-1 ("coved type") ST-segment elevation is considered diagnostic of BrS and it is present either spontaneously or induced by fever or by sodium channel blockers.[5] Drug-induced type 1 Brugada ECG pattern (DI-Type 1 BrP) has been shown to be associated with atrial arrhythmias, atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular accessory pathways (AV-APs) in particular.[6,7]

Loss-of-function and gain-of-function variants in *SCN5A* gene and *SCN1B* locus among BrS susceptibility genes, identified in population-based IBS cohorts have been proposed to have a mechanistic role in the pathophysiology of IBS.[8,9] Loss-of-function variants in *SCN5A*, *SCN1B*, *SCN2B* and *SCN3B* genes encoding the pore-forming α subunit and the β1/β1B/β2/β3 subunits of the cardiac sodium channel ($Na_v1.5$) at 3p21,

19q13.11, 11q23 and 11q23.3 respectively, have been causally related to BrS in ~20-25% of cases.[5] In view of these observations, we extrapolated these findings to our BrS/DI-Type 1 BrP cohort. The present study was designed to determine the period prevalence of FBDs, the prevalence of *SCN5A* and *SCN1B* gene variants, to investigate the demographic and clinical characteristics in probands with BrS/DI-Type 1 BrP and control group and to identify subset of clinical variables to predict underlying BrS/DI-Type 1 BrP among patients with FBDs.

Materials and Methods

Study Population

Two hundred eighty-eight consecutive, unrelated patients and control subjects were included in a single-center, cross-sectional study between September 11th 2018 and November 20th 2018. Sixteen patients were excluded due to following reasons: incomplete filling of questionnaire (n=6), familial Mediterranean fever (n=3), inflammatory bowel disease (n=2), microscopic colitis (n=1), celiac disease (n=1), diverticular disease/colorectal polyps (n=1), spina bifida (n=1) and drug-induced thyrotoxicosis (n=1). The remaining 272 patients (126 women/146 men; mean age 41.8±11.8 years; range 18 to 72) formed the study population. Period prevalence (past 12 months) of FBDs and demographic/clinical characteristics were compared between probands with BrS/DI-Type 1 BrP (n=148, 62 women/86 men; mean age 42.8±11.4; range 18 to 72) and the control group (n=124, 64 women/60 men; mean age 40.6±12.1; range 18 to 66). Prevalence of putative *SCN5A* and *SCN1B* gene variants were screened in 88 patients. The control group consisted of patients with AVNRT (n=24, 19 women/5 men; mean age 46.9±11.1; range 20 to 65), AV-APs (n=42, 17 women/25

men; mean age 36.9±13; range 18 to 66) and "pure" control subjects (n=58, 28 women/ 30 men; mean age 40.7±10.7 years; range 18 to 63) with negative ajmaline challenge test. All study subjects were of Turkish (Anatolian Caucasian) descent. Study protocol was approved by the ethics committee of Ege University School of Medicine (Authorization Number:18-9/49). All patients agreed to participate in the study and gave written informed consent.

Definition of Brugada Syndrome and Drug-Induced Type 1 Brugada ECG Pattern

Ege University School of Medicine BrS/DI-Type 1 BrP cohort consisted of 246 patients referred to our tertiary referral hospital between January 2004 and November 2018. BrS was defined according to the J-Wave syndromes expert consensus conference report.[5] Diagnosis of probable and/or definite BrS, possible BrS, or a nondiagnostic score were assigned scores of ≥3.5, 2 to 3, and <2 points, respectively.[2] Type 1 BrP in at least one right precordial lead during ajmaline challenge test with an assigned score of zero was defined as DI-Type 1 BrP. The proportions of diagnostic types in BrS/DI-Type 1 BrP cohort in the current study were as follows: probable and/or definite BrS (n=17), possible BrS (n=67), nondiagnostic BrS (n=7) and DI-Type 1 BrP (n=57).

Definition of AVNRT, AV-APs and "Pure" Control Groups

All patients with AVNRT and AV-APs underwent electrophysiologic study, catheter ablation and ajmaline challenge test with negative results for type 1 Brugada pattern at our center. The "pure" control group consisted of unrelated subjects with structurally normal hearts, no known heart disease and no history of any type of atrial

arrhythmia including AVNRT, AVRT, preexcitation and atrial fibrillation or any form of ventricular arrhythmia.

Definition of Functional Bowel Disorders

FBDs were defined according to the Rome III diagnostic criteria.[10] The validated Turkish version of the questionnaire (27 questions) with pre-tested psycholinguistic and psychometric properties was used.[11] FBDs were classified into 5 distinct categories: irritable bowel syndrome (IBS), functional constipation, functional diarrhea, functional abdominal bloating/distention, and unspecified FBD.[10] IBS was subcategorized into four subtypes based on predominant stool pattern: constipation (IBS-C), diarrhea (IBS-D), a mix of constipation and diarrhea (IBS-M), or undefined predominant stool form (IBS-U).[10]

Presence of current and/or history of familial Mediterranean fever, inflammatory bowel disease, celiac disease, gastrointestinal or other malignancies except basocellular skin carcinoma, diverticular disease and/or colorectal polyps, history of major abdominal surgeries and/or cholecystectomy, uncontrolled diabetes mellitus, hypothyroidism/hyperthyroidism and chronic opiate and/or any other medication use related with the study were considered as exclusion criteria for the study. Patients were questioned for the presence of “warning” symptoms (evidence of rectal bleeding in the absence of documented bleeding hemorrhoids or anal fissures, unintentional weight loss, family history of colorectal cancer) for consultation by a gastroenterologist.

Period prevalence of FBDs was defined as the proportion of the study subjects who has the characteristics at any point during a given time period of interest (past 12 months).

Acquisition of Data

A total of 306 patients and control subjects were initially contacted by telephone at random in order to question their interest to participate in the study. Eighteen patients declined to participate. All patients and control subjects interested to participate in the study were invited to our medical center and informed about the questionnaire in a face-to-face interview. Participants were encouraged to complete the questionnaire by themselves and mark the most suitable answer in each question by taking enough time.

The final category of the FBDs of each patient was classified based on the flowchart of the questionnaire by co-authors (ASS and SB) blinded to the groups of study population. All patients and control subjects with the diagnosis of FBDs based on the questionnaire were subsequently further questioned for confirmation for the diagnosis and the category of FBDs, subtypes of IBS and history of gastrointestinal work-up after completion of the questionnaire.

History of co-morbid conditions such as structural heart diseases (coronary artery disease, rheumatic heart disease and congenital heart disease), diabetes mellitus, systemic hypertension, epilepsy and migraine were obtained in all participants. Lifetime prevalence of migraine was defined as the proportion of the study subjects who, at some point in life has ever had migraine.

Ajmaline Challenge Test

Ajmaline challenge test (Gilurytmal®, CARINOPHARM GmbH, Germany) was performed according to the J-Wave syndromes expert consensus conference report.[5]

Genetic Screening and In Silico Functional Prediction of Variants

Genetic screening and analysis for *SCN5A* and *SCN1B* gene variants were performed in 88 patients (44 women/44 men; mean age 41±13 years): 57 with BrS/DI-Type 1 BrP and 31 control subjects. *SCN5A* and *SCN1B* gene variants were screened and analyzed by target gene in-depth sequencing by using the Agilent SureSelect Target Enrichment Kit (Agilent Genomics, Santa Barbara, California, USA) and the Illumina Hi-Seq 4000 machine. The identified variants were confirmed by Sanger sequencing. We compared the allele frequency of each identified variant in public databases including 1000 Human Genome Project Database (1000G), Genome Aggregation Database (gnomAD version 2.0.2) and NHLBI GO Exome Sequencing Project (ESP). Functional prediction with two well-known bioinformatics algorithms were used to assess the potential functional impacts of identified mutations, including Sorting Intolerant From Tolerant (SIFT) and Polymorphism Phenotyping-2 (PolyPhen-2). A rare variant was defined as a variant with a minor allele frequency of <0.01%.

Statistical Analysis

Normally distributed variables were presented as mean ± standard deviation and compared using Student's *t*-test. Non-normally distributed variables were presented as median and compared using Mann-Whitney *U* test. Categorical variables were compared using Pearson's chi-squared and Fisher's exact test. Comparisons were performed using Pearson's chi-squared test and univariate logistic regression analysis. In order to identify the predictors for underlying BrS/DI-Type 1 BrP among patients with FBDs, multiple (full model) logistic regression analysis and backward method of stepwise logistic regression analysis were performed with clinical variables

demonstrating significant association on univariate logistic regression analysis. $P < 0.05$ (two-sided) was considered statistically significant.

Results

Demographic/Clinical Characteristics and Prevalence of Functional Bowel Disorders

There were a total of 94 (34.5%) patients with FBDs diagnosed based on the initial flowchart of the questionnaire in the whole study population. The diagnosis of FBDs was dropped out in 3 out of 94 (3.2%) patients and 5 out of 94 (5.3%) patients had a change in the category of FBDs following subsequent questioning of each patient with FBDs by co-authors.

Prevalence of FBDs (43.2% versus 21.8%, $p=1.86\times10^{-4}$) and IBS (25% versus 8.1%, $p=2.34\times10^{-4}$) was higher in patients with BrS/DI-Type 1 BrP compared to the control group, respectively (Table 1). Prevalence of functional constipation, functional diarrhea, functional abdominal bloating/distension and combination of functional constipation/diarrhea/abdominal bloating-distension were not statistically different between patients with BrS/DI-Type 1 BrP and the control group.

The BrS/DI-Type 1 BrP cohort was matched to the control group in terms of age, female sex, presence of arrhythmia and co-morbid conditions (Table 1). The BrS/DI-Type 1 BrP cohort had higher lifetime prevalence of migraine (64.9% versus 29.8%, $p=8.64\times10^{-9}$) compared to the control group (Table 1). None of the patients and control subjects had “warning” symptoms.

There was no statistical difference in terms of mean age (41.7±10.7 years versus 43.8±11.2 years, p=0.387), female sex (46.9% versus 51.9%, p=0.664) and co-morbid

conditions (31.3% versus 15%, p=0.155) among patients with FBDs with BrS/DI-Type 1 BrP and the control group, respectively. Patients with BrS/DI-Type 1 BrP and FBDs had higher lifetime prevalence of migraine (71.9% versus 48.1%, p=0.030) compared to the control group with FBDs, respectively. Among patients with FBDs, prevalence of IBS (57.8% versus 37%, p=0.070) and combination of functional constipation/diarrhea/abdominal bloating-distension (42.2% versus 63%, p=0.070) was not statistically different between patients with BrS/DI-Type 1 BrP and the control group, respectively.

Univariate, multivariable logistic regression analysis and multivariable backward method of stepwise logistic regression analysis were performed to identify subset of clinical variables to predict underlying BrS/DI-Type 1 BrP among patients with FBDs. On stepwise logistic regression analysis, presence of current and/or history of migraine (OR of 2.75; 95% CI: 1.08 to 6.98; p=0.033) was a predictor of underlying BrS/DI-Type 1 BrP.

Genetic Characteristics

We identified 8 putative variants in *SCN5A* and *SCN1B* genes in 7 out of 57 patients with BrS/DI-Type 1 BrP and 1 out of 31 patients in control group (12.3% versus 3.2%, p=0.158), respectively. Demographic, clinical and *SCN5A* and *SCN1B* variant characteristics are presented in Table 2. Five out of 8 (62.5%) patients with *SCN5A* and *SCN1B* variants had FBDs. The prevalence of *SCN5A* and *SCN1B* variants in BrS/DI-Type 1 BrP patients with FBDs (n=25) was not statistically different from control group (n=7) (20% versus 0%, p=0.56), respectively.

Discussion

IBS is a common disabling FBD.[12] Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts.[12] There are several important aspects of the correlation between IBS and BrS/ DI-Type 1 BrP. First is the high prevalence of IBS among patients with BrS/ DI-Type 1 BrP and the epidemiology of both diseases; second is the clinical implications of co-morbidity of IBS; third is the clinical implications of migraine as a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs; and fourth is the underlying genetic characteristics and the mechanistic link between FBDs and BrS/DI-Type 1 BrP, as discussed below.

Epidemiology of Functional Bowel Disorders and BrS/DI-Type 1 BrP

An analysis from a global epidemiological study for functional gastrointestinal disorders, including data from 29.609 adults surveyed in 14 countries, estimated a 10.1% prevalence of IBS based on the Rome III diagnostic criteria. The prevalence of IBS was 9.8% in Turkish population.[2]

The world-wide prevalence of a Brugada ECG pattern (type 1, 2 and 3) in the general population is estimated to be 0.5 to 1.6 per 1000.[5] The prevalence of DI-Type 1 BrP in the general population is unknown. The prevalence of DI-Type 1 BrP in Turkish population was 4.8%.[7] Prevalence of IBS among patients with BrS/DI-Type 1 BrP was 25% in our study. The 25% of the 4.8% of the Turkish population with BrS/DI-Type 1 BrP (~1% of the general population) may have co-occurring IBS and BrS/DI-Type 1 BrP. Prevalence of IBS in Turkish general population and in our control group is ~10%. If these results could be extrapolated to the entire IBS population, we estimate that there

would be nearly 1 in every 10 patients with IBS in general population may have underlying BrS/DI-Type 1 BrP.

Clinical Implications of Co-morbidity of Irritable Bowel Syndrome

IBS was a common co-morbidity in patients with BrS/DI-Type 1 BrP in our study. As a result, each patient with BrS and/or DI-Type 1 BrP should be questioned routinely for the presence and severity of symptoms of IBS during history taking. As documented in our study, certain clinical variables among patients with FBDs such as presence of current and/or history of migraine should raise the possibility of underlying BrS and/or DI-Type 1 BrP.

The coexistence of FBDs/IBS and BrS/DI-Type 1 BrP is of potential clinical relevance for the appropriate management of those patients in terms of cautious use of certain drugs known to exacerbate the Brugada phenotype as reported by the international database (http://www.BrugadaDrugs.org).[13] Among the therapeutic options for IBS, certain drugs (prescribed off-label) with cardiac I_{Na} channel blocking properties such as tricyclic antidepressants and certain selective serotonin reuptake inhibitors (fluoxetine and paroxetine) used for abdominal pain are classified as “to be avoided” or “preferably avoided” in patients with BrS.[13] Drugs (not listed in the international database) with potential cardiac I_{Na} and I_{Ks}/ I_{Kr} channel blocking properties such as certain opioid agonists (loperamide) particularly at high doses used for diarrhea is known to be a pro-arrhythmic agent.[14]

Clinical Implications of Migraine as a Predictor of Underlying BrS/DI-Type 1 BrP Among Patients with Functional Bowel Disorders

Patients with IBS are reportedly more likely to have other co-morbidities including migraine, chronic fibromyalgia, and depressive disorders.[15] Lifetime prevalence of migraine in general population is reported to be approximately 30% worldwide.[16] Lifetime prevalence of migraine in Turkish population is reported to be 19.9% among men and 29.3% among women.[17] Our current study showed that the lifetime prevalence of migraine was higher (64.9% versus 29.8%) in patients with BrS/DI-Type 1 BrP compared to the control group. Lifetime prevalence of migraine was even higher (71.9% versus 48.1%) in patients with BrS/DI-Type 1 BrP and FBDs compared to the control group with FBDs. Co-occurrence (bidirectional co-morbidity) of IBS, BrS/DI-Type 1 BrP and migraine may represent a genetic overlap. The identification of genetic overlap and specific genetic variants shared across these disorders can be used to assess the validity of the clinical diagnosis and classification of patients.

The Co-morbidity of Irritable Bowel Syndrome and BrS/DI-Type 1 BrP: Causation, Correlation, or Confound?

Many different models have been proposed to explain the co-occurrence of two or more disorders in the same individual.[18] The direct causation model states that one disorder causes or lowers the threshold for the expression of the other disorder. This model can be proven by large population studies with long-term follow-up rather than clinical studies. The shared etiology (correlation) model posits that a common set of risk factors leads to the development of co-morbid diseases.[18] We hypothesized that IBS and BrS/DI-Type 1 BrP co-occur because they share a common genetic background.

Underlying mechanisms that could lead to IBS include genetic factors (most notably *SCN5A* mutations); disturbances in the intestinal microbiota; low-grade mucosal inflammation, disordered bile salt metabolism; abnormalities in serotonin metabolism; and alterations in brain function.[19] IBS is known to aggregate in families.[20] Familial aggregation may be due to shared genetic or environmental factors.[21] BrS and IBS are genetic diseases and share common features such as oligogenic/polygenic genetic architecture, same causal common and/or rare variants and worsening of phenotype by gene dysregulation induced by environmental factors (fever and drugs in patients with BrS and certain foods or beverages and hormones in patients with IBS).[5,8,9,22,23]

Electromechanical organs, such as the heart and gastrointestinal tract, are electrically excitable tissues with a primary mechanical function.[24] Coordinated electrical activity in the gastrointestinal tract requires the interaction of several cell types, including intrinsic and extrinsic enteric neurons, interstitial cells of Cajal (ICC) and smooth muscle cells (SMC).[24] Human ICCs generate pacemaker activity through slow electrical waves and are electrically coupled to smooth muscle cells (SMC) via gap junctions ensuring coordinated gastrointestinal motility. The voltage sensitive and the mechanosensitive Na^+ channels (Nav1.5) highly expressed in human cardiac myocytes as well as human intestinal ICC and SMC are among the ion channels involved in gastrointestinal motility.[25-27] The pore-forming α subunit of the voltage-dependent sodium channel ($Na_v1.5$), encoded by the *SCN5A* gene is the predominant gastrointestinal Na_v isoform.[28] Human gastrointestinal $Na_v1.5$ is structurally homologous to its cardiac equivalent and shares strong electrophysiological, mechanosensitive, and pharmacological similarities.[28]

The cardiac Na^+ channel complex is composed of a primary α and multiple ancillary β subunits.[29] $Na_v1.5$ α subunit encoded by the *SCN5A* gene is the predominantly expressed voltage-gated sodium channel in cardiac myocytes and the primary contributor to recorded sodium current (I_{Na}) density.[29] Four auxiliary β subunits ($Na_vβ1$ to $Na_vβ4$, encoded by the genes *SCN1B* to *SCN4B*, respectively) have been identified.[29] The β subunits modulate density, kinetics, voltage dependence of activation and inactivation, as well as surface expression of the Na^+ channel.[29] Loss-of-function variants in *SCN5A*, *SCN1B*, *SCN2B* and *SCN3B* genes encoding the pore-forming α subunit and the β1/β1B/β2/β3 subunits of the cardiac sodium channel ($Na_v1.5$) at 3p21, 19q13.11, 11q23 and 11q23.3 respectively, have been causally related to BrS in ~20-25% of cases.[5]

There is mounting evidence of the association of sodium-channel defects and functional gastrointestinal disorders.[28] Loss-of-function and gain-of-function variants in *SCN5A* gene have been identified in patients with wide-range of gastrointestinal symptoms, FBDs, and functional dyspepsia.[8,30-33] Patients with long QT syndrome type 3 as a result of gain-of-function mutations in *SCN5A* gene have been found to have higher prevalence of gastrointestinal symptoms and IBS compared to mutation negative family members.[30,31] A pilot study identified a loss-of-function missense mutation in *SCN5A* gene in one patient among 49 screened patients with IBS.[32] A subsequent genome-wide association study (GWAS) was performed in 584 patients with IBS and 1380 healthy controls and then replicated in 4 independent cohorts.[8] *SCN5A* missense mutations (mostly loss-of-function) were present in 13 (2.2%) patients with IBS.[8] A greater proportion of patients with *SCN5A* mutation met criteria for IBS-C than for IBS-

D. *SCN5A* loss-of-function mutations in patients with IBS have been shown to generate $Na_V1.5$ currents of smaller density and reduced mechanosensitivity.[8]

Two out of 7 patients with BrS/DI-Type 1 BrP and *SCN5A/SCN1B* variants in our study population (Patient 1 and 2 in Table 2) had loss-of-function *SCN5A* variant (p.Phe1293Ser) and IBS-C. Interestingly, this particular *SCN5A* variant has been previously reported in patients with IBS-C and proposed to have a mechanistic role in the pathophysiology of IBS as a result of decreased $Na_V1.5$ current density and altered voltage-dependent and mechanosensitive functions.[34,35]

Over the past decade, large scale, powered gene mapping studies have made important contributions to identifying genetic components involved in BrS and IBS.[8,9,22] These studies provided further evidence that BrS and IBS are genetically complex in the sense that multiple common variants, with small effect sizes, together with environmental factors confer susceptibility.[8,9,22] A recent GWAS meta-analysis from 5 population-based cohorts implicated ion channel genes in the pathogenesis of IBS. A total of 1335 patients with IBS and 9768 control subjects from 5 independent European cohorts based on questionnaire data compatible with Rome III criteria were genotyped.[9] Suggestive GWAS signals were identified in 7 genomic regions, harboring 64 gene candidates to affect IBS risk via altered function and/or expression of ion channels. Interestingly, one of the suggestive risk loci was *SCN1B* gene on chromosome 19.[9] *SCN1B* gene encodes the β1 and β1B subunits of the cardiac sodium channel which is highly expressed by ICC in the mouse colon.[36] $Na_v1.5$ β1 subunit has been reported to be the predominant voltage-gated sodium channel in murine colonic ICC.[36] Variants in *SCN1B* are linked to BrS/cardiac conduction disease, atrial fibrillation, epilepsy

syndromes and sudden infant death syndrome.[29] Four out of 7 patients with BrS/DI-Type 1 BrP had *SCN1B* variants in our study population (Patients 4-7 in Table 2). Two of those patients had FBDs.

Study limitations

The current Rome IV diagnostic criteria were not used in our study because of lack of validation of the questionnaire in Turkish population. Comparative characteristics of IBS and identification of biological and/or clinical variables that point to an underlying type1-BrP among patients with IBS were not possible between BrS/DI-Type 1 BrP cohort and the control group because of relatively low number of patients with IBS in the control group.

Conclusions

IBS is a common co-morbidity in patients with BrS/DI-Type 1 BrP. Recognition of co-existing BrS/DI-Type 1 BrP among patients with FBDs by using certain clinical variables such as presence of current and/or history of migraine will allow physicians to treat their patients more effectively without exposing them to hidden drug cardiotoxicities. Larger studies are necessary to confirm the co-existence of BrS/DI-Type 1 BrP and IBS and to further define the phenotypical characteristics, the molecular genetic overlap and the role of ajmaline challenge test in these patients.

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Table 1

Demographic and Clinical Characteristics, Prevalence of Functional Bowel Disorders and Gastrointestinal Work-Up Characterisitcs in Patients with Brugada Syndrome/Drug-Induced Type 1 Brugada ECG Pattern and Conrol Group

Variable	Patients with BrS/DI-Type 1 BrP (n=148)	Control Group (n=124)	P-value
Demographic and Clinical Characteristics			
- Age (years):	42.8±11.4	40.6±12.2	0.135
- Sex (Female) (%):	62 (41.9)	64 (51.6)	0.109
- Presence of Arrhythmia (%):	75 (50.7)	66 (53.2)	0.675
- Presence of Co-Morbid Conditions (%):	46 (31.1)	17 (25.8)	0.430
- Presence of Migraine (%):	96 (64.9)	37 (29.8)	8.64×10^{-9}
Categories of Functional Bowel Disorders			
- Functional Bowel Disorders (%):	64 (43.2)	27 (21.8)	1.86×10^{-4}
- Irritable Bowel Syndrome (%):	37 (25)	10 (8.1)	2.34×10^{-4}
- Constipation subtype (%):	17 (45.9)	7 (70)	0.177
- Diarrhea subtype (%):	11 (29.7)	1 (10)	0.204
- Mix of Constipation and Diarrhea subtype (%):	6 (16.2)	1 (10)	0.624
- Undefined subtype (%):	3 (8.1)	1 (10)	1.000
- Functional Constipation (%):	5 (3.4)	2 (1.6)	0.460
- Functional Diarrhea (%):	3 (2)	2 (1.6)	0.80
- Functional Abdominal Bloating/Distension (%):	19 (12.8)	13 (10.5)	0.548
- Functional Constipation/Diarrhea/Abdominal Bloating/Distension (%):	27 (18.2)	17 (13.7)	0.312
Gastrointestinal Work-Up in Patients with Functional Bowel Disorders*			
- History of Gastointestinal Consultations and Work-Up (%):	38 (59.4)	12 (44.4)	0.191
- History of Upper Endoscopy (%):	24 (37.5)	9 (33.3)	0.706
- History of Colonoscopy (%):	11 (17.2)	2 (7.4)	0.223

Data are given as mean ± SD, number of patients and percentages. * = By Primary Care Physician and/or Gastroenterologist, BrS = Brugada syndrome, DI-Type 1 BrP = Drug-Induced Type 1 Brugada ECG pattern.

Table 2

Summary of Demographic, Clinical and *SCN5A/SCN1B* Gene Variant Characteristics

Patient No.	Age	Sex	Cardiac D_x	Type of FBDs	Gene	Exon	Type and Functio nof Mutatio n	Change in Nucleotide	Change in Amino Acid	MAF (1000genome)	MAF (ESP)	MAF (gnomAD)	SIFT-Prediction	Polyphen-2 Prediction	Gene References
1	31	M	BrS	IBS-C	SCN5A	22	Missense LofF	c.3878T>C	p.Phe1293Ser	NA	NA	0.0005892	Tolerated	Benign	Sommariva E, et al. Cardiogenetics 2012; 2:e1
2	34	F	BrS	IBS-C	SCN5A	22	Missense LofF	c.3878T>C	p.Phe1293Ser	NA	NA	0.0005892	Tolerated	Benign	Sommariva E, et al. Cardiogenetics 2012; 2:e1
3	44	M	BrS	IBS-D	SCN5A	27	Missense Unknown	c.4789G>A	p.Val1597Met	NA	NA	0.0000177	Damaging	Probably Damaging	Hedley PL, et al. Hum Mut 2009;30:1486-1511.
4	32	F	BrS	IBS-C	SCN1B	NA	Intronic Unknown	IVS5+36G>A	NA	NA	NA	NA	NA	NA	NA
5	35	F	DI-Type 1 BrP	Functional AB/D	SCN1B	5	Missense Unknown	c.638G>A	p.Gly213Asp	0.0002	0	0.00001768	Damaging	Possibly Damaging	NA
6	57	M	BrS	None	SCN1B	3	Missense LofF	c.259G>C	p.Glu87Gln	0	0	0.000003978	Tolerated	Benign	Watanabe H, et al. J Clin Invest. 2008;118:2260-226
7	45	F	BrS	None	SCN1B	4	Missense Unknown	c.503T>C	p.Val168Ala	0	0	NA	Tolerated	Benign	Hasdemir C, et al. Heart Rhythm. 2015;12:1584-1594.
8	58	F	Control	None	SCN5A	17	Missense Unknown	c.3067C>T	p.Arg1023Cys	NA	NA	0.00002018	Tolerated	Probably Damaging	Watanabe H, et al. Int J Cardiol. 2013;165:e21-3

BrS = Brugada Syndrome, DI-Type 1 BrP = Drug-Induced Type 1 Brugada Pattern, D_x = Diagnosis, ESP = Exome Sequencing Project, Functional AB/D = Abdominal Bloating/Distension, FBD = Functional Bowel Disorders, gnomAD = Genome Aggregation Database, IBS-C = Irritable Bowel Syndrome Constipation, IBS-D = Irritable Bowel Syndrome Diarrhea, LofF = Loss of Function, MAF = Minor Allele Frequency, 1000 genome = 1000 Human Genome Project Database, Polyphen-2 = Polymorphism Phenotyping 2, SIFT = Sorting Intolerant From Tolerant