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Recognition and Clinical Implications of High Prevalence of Migraine in Patients with Brugada Syndrome and Drug-Induced Type 1 Brugada Pattern

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Structured Abstract

Introduction: We have previously reported high 1-year prevalence of migraine in patients with atrial arrhythmias associated with DI-Type 1 BrP. The present study was designed to determine the lifetime prevalence of migraine in patients with Brugada syndrome (BrS)/drug-induced type 1 Brugada pattern (DI-Type 1 BrP) and control group, to investigate the demographic and clinical characteristics, and to identify clinical variables to predict underlying BrS/DI-Type 1 BrP among migraineurs.

Methods and Results: Lifetime prevalence of migraine and migraine characteristics were compared between probands with BrS/DI-Type 1 BrP (n=257) and control group (n=370). Lifetime prevalence of migraine was 60.7% in patients with BrS/DI-Type 1 BrP and 30.3% in control group ($p=3.6\times10^{-14}$). On stepwise regression analysis, familial migraine (odds ratio [OR] of 4.4; 95% confidence interval [CI]: 2.0 to 9.8; $p=1.3\times10^{-4}$), vestibular migraine (OR of 5.4; 95% CI: 1.4 to 21.0); p=0.013), migraine with visual aura (OR of 1.8; 95% CI: 1.0 to 3.4); p=0.04) and younger age-at-onset of migraine (OR of 0.95; 95% CI: 0.93 to 0.98); p=0.004) were predictors of underlying BrS/DI-Type 1 BrP among migraineurs. Use of anti-migraine drugs classified as “to be

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avoided" or "preferably avoided" in patients with BrS and several other anti-migraine drugs with potential cardiac I_{Na}/I_{Ca} channel blocking properties was present in 25.6% and 26.9% of migraineurs with BrS/DI-Type 1 BrP, respectively.

Conclusion: Migraine co-morbidity is common in patients with BrS/DI-Type 1 BrP. We identify several clinical variables that point to an underlying type1-BrP among migraineurs, necessitating cautious use of certain anti-migraine drugs.

Keywords

Brugada Syndrome; Drug-Induced Type 1 Brugada ECG Pattern; Migraine; Drugs; Epidemiology; Genetics

Introduction

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.[1] 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.[2] 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.[3,4]

Migraine is a common, multifactorial primary headache disorder with a strong genetic component.[5,6] One-year prevalence of migraine is 14.4% worldwide.[7] We have previously reported high 1-year prevalence of migraine in patients with AVNRT and AV-APs associated with DI-Type 1 BrP.[3,4] In view of this observation, we extrapolated this finding to our BrS/DI-Type 1 BrP cohort. The present study was designed to determine the lifetime prevalence of migraine in patients with BrS/DI-Type 1 BrP and control group, to investigate the demographic and clinical characteristics, and to identify subset of clinical variables to predict underlying BrS/DI-Type 1 BrP among migraineurs.

Methods

Study Population

Six hundred twenty-seven consecutive, unrelated patients (301 women/326 men; mean age 47.3±13.9 years; range 17 to 89) were retrospectively included in a case–control observational study between April 2019 and December 2019. Lifetime prevalence of migraine and migraine characteristics were compared between probands with BrS/DI-Type 1 BrP (n=257, 101 women/156 men; mean age 45.6±13.1; range 17 to 85) and control group (n=370, 206 women/164 men; mean age 48.5±14.3; range 18 to 89). The control group consisted of patients with AVNRT (n=213, 141 women/72 men; mean age 52.4±14.8; range 22 to 89), AV-APs (n=77, 26 women/51 men; mean age 41.2±11.5; range 22 to 66) and "pure" control subjects (n=80, 39 women/41 men; mean age 39±11 years; range 18 to 63) with negative ajmaline challenge test (ACT). All study subjects were of Turkish (Anatolian Caucasian) descent. Study protocol was approved by the Ethics Committee of Ege

University School of Medicine. 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

BrS was defined according to the J-Wave syndromes expert consensus conference report.[2] 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 ACT with an assigned score of zero was defined as DI-Type 1 BrP.

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

All patients with AVNRT and AV-APs underwent electrophysiologic study, catheter ablation and ACT 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. Four out of 84 (4.8%) "pure" control subjects developed type 1 Brugada pattern with ACT and were included in the DI-Type 1 BrP group for the final statistical analysis.

Definition of Migraine and Migraine Characteristics

All patients and control subjects were initially screened by telephone using a validated questionnaire (consisting of 4 questions) designed to screen the general population for migraine.[8] Those who, answered "yes" to at least one of 4 questions were invited to participate in a face-to-face interview. Migraine was defined according to the international classification of headache disorders-3 (ICHD-3) criteria.[9] Demographic, clinical and migraine characteristics were obtained by using a structured questionnaire (25 items) to ensure that each interview is presented with exactly the same questions in the same order. The questionnaire consisted of 8 sections: 1- Demographic and clinical data, including age, sex, medical history, and risk factors. 2- Age-at-onset of migraine. 3- Headache characteristics (frequency, duration, intensity, quality, location, accompanying symptoms, triggering factors). 4- Presence of aura and aura characteristics. 5- Presence of familial migraine and probands experience in diagnosing migraine. 6- Presence of vestibular symptoms accompanying migraine. 7- Prior diagnosis of primary headache, based on the diagnosis conducted by a primary physician or a neurologist. 8- List of anti-migraine drugs. Sixteen patients (6.2%) in BrS/DI-Type 1 BrP cohort and 21 patients (5.7%) in control group were interviewed via social media due to living at long-distance. Lifetime prevalence of migraine was defined as the proportion of the study subjects who, at some point in life has ever had migraine.

Migraine with aura (ICHD-3/1.2) was defined as transient focal neurological symptoms that usually precede or sometimes accompany the headache. Aura symptoms were classified as visual, sensory, speech and/or language, motor, brainstem and retinal. Visual aura characteristics such as unilaterality, presence of scotoma, fortification and/or flickering light, small bright dots, "foggy" vision, "like looking through heat waves or water" and total duration were obtained. Sensory aura characteristics such as unilaterality, affected areas of the body, and total duration were obtained. Chronic migraine was defined according to both

ICHD-3 criteria (1.3) and recently proposed new diagnostic criteria.[9,10] Vestibular migraine (ICHD-3/A1.6.6) was defined as presence of vestibular symptoms of moderate or severe intensity associated with migraine (current or past history) in at least half of episodes. Patients with age-at-onset of migraine of 18-year-old or younger were considered to have pediatric migraine. Familial migraine was defined as presence of ≥1 first-degree relative(s) of probands with migraine.[11]

Acquisition of Data

Our observational BrS/DI-Type 1 BrP cohort consisting of 264 patients referred to our tertiary referral hospital between January 2004 and December 2019. Seven patients were excluded due to loss to follow-up. The remaining 257 patients formed the BrS/DI-Type 1 BrP cohort (probable and/or definite BrS [n=36], possible BrS [n=110], nondiagnostic BrS [n=11] and DI-Type 1 BrP [n=100]).

Family screening with ACT as part of our genetic studies for BrS was performed in a total of 115 first degree relatives (57 women/58 men; mean age 47±10.9; range 16 to 77) of 61 probands in BrS/DI-Type 1 BrP cohort and their history of migraine were obtained.

Patients with AVNRT and AV-APs were initially screened for migraine during systematic questioning for co-morbid conditions prior to catheter ablation.

Patients with symptoms suggestive of secondary headache (new-onset headache particularly in persons older than 50 years of age, and vision/sensory/language symptoms lasting >1 hour), equivocal symptoms of cluster and tension-type headache and symptoms of brainstem and retinal aura were consulted by a headache specialist (FG).

A detailed history of anti-migraine drugs for acute and/or prophylactic therapy was obtained in all patients. Drugs classified as “to be avoided” or “preferably avoided” in patients with BrS (http://www.BrugadaDrugs.org) and drugs with potential cardiac I_{Na} and I_{Ca} channel blocking properties were noted.[12,13]

Ajmaline Challenge Test

ACT (Gilurytmal®, CARINOPHARM GmbH, Germany) was performed according to the J-Wave syndromes expert consensus conference report.[2] Indications for ACT were as follows: presence of symptoms (transient loss-of-consciousness, palpitations and/or chest pain) with baseline type 2 or 3 BrP (n=83 [14.3%]), verification of type 1 BrP in coincidentally discovered patients with baseline type 2 or 3 BrP (n=22 [3.8%]), cascade screening in families with history of sudden death in the young (≤ 40 years) in first degree relatives (n=3 [0.5%]) and research protocol for patients and subjects with AVNRT, AV-APs and “pure” control group (n=473 [81.4%]).

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 migraineurs, multivariable (full model) logistic regression analysis and multivariable forward 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 Characteristics and Lifetime Prevalence of Migraine

Mean age of patients with BrS/DI-Type 1 BrP and control group was 45.6±13.1 years and 48.5±14.3 years (p=0.008), respectively. Male sex was more common in patients with BrS/DI-Type 1 BrP compared to control group (60.7% versus 44.3%, $p=5.5\times10^{-5}$). The proportion of male sex in subgroups of BrS/DI-Type 1 BrP cohort and control groups was as follows: probable and/or definite BrS (86.1%), possible BrS (79.1%), nondiagnostic BrS (54.5%), DI-Type 1 BrP (32%), AVNRT (33.8%), AV-APs (66.2%) and “pure” control group (51.2%). Average duration of follow-up was 66.6±29.2 months (median 69/range 8 to 201) and 64.6±18.7 months (median 70/range 8 to 103) in patients with BrS/DI-Type 1 BrP and control group, respectively.

Lifetime prevalence of migraine was 60.7% in patients with BrS/DI-Type 1 BrP and 30.3% in control group ($p=3.6\times10^{-14}$). Sex-adjusted analysis revealed that lifetime prevalence of migraine among females with BrS/ DI-Type 1 BrP was higher compared to female controls (85.1% versus 39.8%, $p=6.4\times10^{-14}$). Lifetime prevalence of migraine among males with BrS/ DI-Type 1 BrP was higher compared to male controls (44.9% versus 18.3%, $p=2.9\times10^{-7}$).

Lifetime prevalence of migraine between subgroups of BrS/DI-Type 1 BrP cohort was as follows: probable and/or definite BrS (44.4%), possible BrS (59.1%), nondiagnostic BrS (72.7%) and DI-Type 1 BrP (67%, p=0.092). Lifetime prevalence of migraine between subgroups of control group was as follows: AVNRT (32.4%), AV-APs (33.8%) and “pure” control group (21.3%, p=0.136).

Demographic and Clinical Characteristics of Migraineurs, Choices of Anti-Migraine Drug Therapy and Proarrhythmia

Demographic and clinical characteristics of migraineurs and choices of anti-migraine drug therapy in patients with BrS/DI-Type 1 BrP and control group are presented in Table 1.

Univariate, multivariable logistic regression analysis and multivariable forward method of stepwise logistic regression analysis performed to identify subset of clinical variables to predict underlying BrS/DI-Type 1 BrP among migraineurs are presented in Table 2. On multivariable logistic regression analysis, familial migraine (odds ratio [OR] of 3.8; 95% confidence interval (CI): 1.5 to 9.7; p=0.004) and vestibular migraine (OR of 5.1; 95% CI: 1.4 to 19.0); p=0.015) were predictors of underlying BrS/DI-Type 1 BrP. On stepwise logistic regression analysis, familial migraine (OR of 4.4; 95% CI: 2.0 to 9.8; $p=1.3\times10^{-4}$), vestibular migraine (OR of 5.4; 95% CI: 1.4 to 21.0); p=0.013), migraine with visual aura

(OR of 1.8; 95% CI: 1.0 to 3.4); p=0.04) and younger age-at-onset of migraine (OR of 0.95; 95% CI: 0.93 to 0.98); p=0.004) were predictors of underlying BrS/DI-Type 1 BrP.

Current or history of use of anti-migraine drugs classified as “to be avoided” or “preferably avoided” in patients with BrS (ergot alkaloids [n=32], tricyclic antidepressants [n=6], certain selective serotonin reuptake inhibitors [fluoxetine and paroxetine][n=9], certain anti-epileptic agents [carbamazepine][n=1], and propranolol [n=1]) was present in 40 (25.6%) migraineurs with BrS/DI-Type 1 BrP. Current or history of use of anti-migraine drugs (not listed in the international database) with potential cardiac I_{Na} and I_{Ca} channel blocking properties (certain serotonin-noradrenaline reuptake inhibitors [duloxetine][n=5], certain anti-epileptic agents [gabapentin, topiramate and pregabalin][n=6] and certain nonsteroidal anti-inflammatory drugs [diclofenac][n=37]) was present in 42 (26.9%) migraineurs with BrS/DI-Type 1 BrP.

Drug-induced initiation (paroxetine, n=1) and/or worsening (duloxetine, n=4, fluoxetine, n=1, gabapentin, n=1, pregabaline, n=1, risperidone, n=1, and carbamazepine; n=1) of duration and/or frequency of palpitations (along with documented AVNRT [n=6] or frequent, monomorphic premature ventricular contractions and/or nonsustained ventricular tachycardia [n=2]) during therapy with anti-migraine drugs were observed in 8 (5.1%) migraineurs with BrS/DI-Type 1 BrP. There was no life-threatening arrhythmic event potentially related to the use of anti-migraine drugs.

Family Screening with ACT and Migraine Co-morbidity

Family screening with ACT revealed good correlation between the positivity of ACT and presence or absence of current or history of migraine. The proportion of subgroups of ACT (+)/Migraine (+), ACT (+)/Migraine (−), ACT (−)/Migraine (+) and ACT (−)/Migraine (−) were 50.4%, 12.2%, 14.8% and 22.6% ($p=8.0\times10^{-6}$), respectively.

Discussion

Migraine is a common disabling primary headache disorder.[14] Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts.[14] There are several important aspects of the strong correlation between migraine and BrS/ DI-Type 1 BrP. First is the high lifetime prevalence of migraine among patients with BrS/ DI-Type 1 BrP and the epidemiology of both diseases; second is the clinical implications of migraine co-morbidity; and third is the underlying genetic characteristics and the mechanistic link between migraine and BrS/DI-Type 1 BrP, as discussed below.

Epidemiology of Migraine and BrS/DI-Type 1 BrP

An analysis from the 2016 Global Burden of Disease study, including data from 132 countries, estimated that worldwide 1.04 billion people had migraine, corresponding to a 1-year prevalence of 14.4% overall, 18.9% in women, and 9.8% in men.[7] One-year prevalence of migraine was 16 to 17% in Turkish population.[7] Lifetime prevalence of migraine in Turkish population assessed by face-to-face interviews was reported to be 19.9% among men and 29.3% among women.[15] Lifetime prevalence of migraine is reported to be approximately 30% worldwide.[14]

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.[2] The prevalence of DI-Type 1 BrP in the general population is unknown. The prevalence of DI-Type 1 BrP in our control group was 4.8%. Lifetime prevalence of migraine among patients with BrS/DI-Type 1 BrP was 60.7% in our study. The 60.7% of the 4.8% of the Turkish population with BrS/DI-Type 1 BrP (~3% of the general population) may have co-occurring migraine and BrS/DI-Type 1 BrP. Lifetime prevalence of migraine in our control group is approximately 30%. If these results could be extrapolated to the entire migraine population, we estimate that there would be nearly 1 in every 10 migraineurs in general population may have underlying BrS/DI-Type 1 BrP.

Clinical Implications of Migraine Co-morbidity

As documented in our study, certain clinical variables among migraineurs such as familial migraine, vestibular migraine, migraine with visual aura and younger age-at-onset of migraine should raise the possibility of BrS and/or DI-Type 1 BrP.

The coexistence of migraine 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 anti-migraine drugs known to exacerbate the Brugada phenotype as reported by the international database (http://www.BrugadaDrugs.org).[12] In our study, the rates of current or history of use of anti-migraine drugs classified as “to be avoided” or “preferably avoided” in patients with BrS and several other anti-migraine drugs (not listed in the international database) with potential cardiac I_{Na} and I_{Ca} channel blocking properties in migraineurs with BrS/DI-Type 1 BrP were 25.6% and 26.9%, respectively.

Causation, Correlation, or Confound: What the Co-morbidity of Migraine and BrS/DI-Type 1 BrP can Tell Us about the Etiology of These Genetic Diseases?

Many different models have been proposed to explain the co-occurrence of two or more disorders in the same individual.[16] 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.[16] We hypothesized that migraine and BrS/DI-Type 1 BrP co-occur because they share a common genetic background. Three migraine characteristics in patients with BrS/DI-Type 1 BrP in our study support the shared etiology model: 1- High (91%) prevalence of familial migraine, 2- Good correlation between positivity of ACT for type 1 Brugada ECG pattern and presence of migraine among first degree relatives of probands (the proportion of sum of ACT (+)/Migraine (+) and ACT (−)/Migraine (−) subgroups equals to 73%), and 3- Induction of migraine-type headache during ACT in 7.9% of migraineurs.

BrS and migraine 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 drugs and hormones in patients with migraine).[2,17–20]

Over the past decade, genome-wide association studies (GWAS) have made important contributions to identifying genetic components involved in BrS and migraine.[18,20] These studies provided further evidence that BrS and common types of migraine are genetically complex in the sense that multiple common variants, with small effect sizes, together with environmental factors confer susceptibility.[6,18–20] Rare variants with large effect sizes determined by polygenic risk score analysis may have substantial contributions to the pathogenesis as shown by recent studies.[17] Loss-of-function mutations in *SCN5A*, encoding the pore-forming subunit of the cardiac sodium channel ($Na_v1.5$) at 3p21, have been causally related to the disease in ~20% of cases with BrS.[19] Mutations in genes other than *SCN5A* have been found in a small subset of cases.[19] There are 4 common variants (minor allele frequency >5%) and 1 rare variant (minor allele frequency <1%) in 5 different genes implicated as causal genetic variants in both BrS and migraine reported in the literature. Causal genetic variants are as follows: 1- *Hey2*, encoding a NOTCH-dependent transcription factor, 2- *SCN5A* affecting expression of I_{Na} currents, 3- *CACNB2* affecting expression of I_{Ca} currents, and 4- *KCNE2* and *KCNK17* affecting expression of I_{to} and I_K currents, respectively.[17,18,20–24]

Study limitations

BrS/DI-Type 1 BrP cohort was not matched to the control group in terms of age and gender due to nature of the patient populations. There is recall bias in history taking for lifetime migraine and choices of anti-migraine drugs.

Conclusions

Migraine co-morbidity is common in patients with BrS/DI-Type 1 BrP. Recognition of co-existing BrS/DI-Type 1 BrP among migraineurs by using certain clinical variables such as familial migraine, vestibular migraine, migraine with visual aura and younger age-at-onset 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 migraine and to further define the phenotypical characteristics, the molecular genetic overlap and the role of ACT in these patients.

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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. [PubMed: 1309182]
2. Antzelevitch C, Yan GX, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Heart Rhythm 2016;13:e295–e324. [PubMed: 27423412]
3. Hasdemir C, Payzin S, Kocabas U, et al. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. Heart Rhythm 2015;12:1584–1594. [PubMed: 25998140]

4. Hasdemir C, Juang JJ, Kose S, et al. Coexistence of atrioventricular accessory pathways and drug-induced type 1 Brugada pattern. Pacing Clin Electrophysiol 2018;41:1078–1092. [PubMed: 29953624]
5. Charles A. Migraine. N Engl J Med 2017;377:553–561. [PubMed: 28792865]
6. Nyholt DR, van den Maagdenberg AM. Genome-wide association studies in migraine: current state and route to follow. Curr Opin Neurol 2016;29:302–308. [PubMed: 26967494]
7. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:954–976. [PubMed: 30353868]
8. Gervil M, Ulrich V, Olesen J, Russell MB. Screening for migraine in the general population: validation of a simple questionnaire. Cephalalgia 1998;18:342–348. [PubMed: 9731939]
9. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.
10. Chalmer MA, Hansen TF, Lebedeva ER, Dodick DW, Lipton RB, Olesen J. Proposed new diagnostic criteria for chronic migraine. Cephalalgia 2020;40:399–406. [PubMed: 31544467]
11. Ravn J, Chalmer MA, Oehrstroem EL, Kogelman LJA, Hansen TF. Characterization of familial and sporadic migraine. Headache 2019;59:1802–1807. [PubMed: 31544229]
12. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;6:1335–1341. [PubMed: 19716089]
13. Ferdinandy P, Baczkó I, Bencsik P, et al. Definition of hidden drug cardiotoxicity: paradigm change in cardiac safety testing and its clinical implications. Eur Heart J 2019;40:1771–1777. [PubMed: 29982507]
14. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. Neurol Clin 2019;37:631–649. [PubMed: 31563224]
15. Celik Y, Ekuklu G, Tokuc B, Utku U. Migraine prevalence and some related factors in Turkey. Headache 2005;45:32–36. [PubMed: 15663610]
16. Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. Am J Hum Genet 1995;57:935–953. [PubMed: 7573055]
17. Techlo TR, Rasmussen AH, Møller PL, et al. Familial analysis reveals rare risk variants for migraine in regulatory regions. Neurogenetics 2020;21:149–157. [PubMed: 32076896]
18. Bezzina CR, Barc J, Mizusawa Y, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet 2013;45:1044–1049. [PubMed: 23872634]
19. Aiba T Recent understanding of clinical sequencing and gene-based risk stratification in inherited primary arrhythmia syndrome. J Cardiol 2019;73:335–342. [PubMed: 30910390]
20. Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 2016;48:856–866. [PubMed: 27322543]
21. Nyholt DR, LaForge KS, Kallela M, et al. A high-density association screen of 155 ion transport genes for involvement with common migraine. Hum Mol Genet 2008;17:3318–3331. [PubMed: 18676988]
22. Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation 2007;115:442–449. [PubMed: 17224476]
23. Wu J, Shimizu W, Ding WG, et al. KCNE2 modulation of Kv4.3 current and its potential role in fatal rhythm disorders. Heart Rhythm 2010;7:199–205. [PubMed: 20042375]
24. Friedrich C, Rinné S, Zumhagen S, et al. Gain-of-function mutation in TASK-4 channels and severe cardiac conduction disorder. EMBO Mol Med 2014;6:937–951. [PubMed: 24972929]

Table 1

Comparison of Demographic and Clinical Characteristics of Migraineurs and Choices of Anti-Migraine Drug Therapy in Patients with Brugada Syndrome/Drug-Induced Type 1 Brugada ECG Pattern and Conrol Group

Variable	Patients with BrS/DI-Type 1 BrP (n=156)	Control Group (n=112)	P-value
Demographic and Clinical Characteristics			
- Age (years):	43.9±12	46±12.9	0.174
- Age-at-onset of migraine (years):	21.2±10.3	26.5±10.3	9.0×10^{-5}
- Sex (Female) (%):	55.1	73.2	0.003
- Pediatric migraine (%):	47.3	23.6	1.3×10^{-4}
- Frequency of migraine (days/month):	5 (Median-/Range 1 to 30)	3 (Median-/Range 1 to 30)	0.007
- Duration of migraine:			
- 4–12 hours/12–24 hours/Days (%):	36.9/26.2/36.9	39/33.3/27.6	0.251
- Intensity of migraine (VAS):	4 (Median-/Range 2 to 5)	3.5 (Median-/Range 2.5 to 5)	0.224
- Chronic migraine:			
- ICHD-3 criteria (%):	19.6	10.5	0.054
- Proposed new diagnostic criteria (%):	33.1	20	0.023
- Triggers of migraine:			
- Emotional stress (%):	50.3	32.4	0.005
- Skipping meals (%):	31.3	18.1	0.018
- Menstruation (%):	26.8	34.2	0.311
- Seasonal factors (%):	20.4	9.5	0.020
- Lack of sleep (%):	32.7	24.8	0.175
- Others (%):	17.7	8.6	0.039
- Accompanying symptoms:			
- Photophobia (%):	81.6	78.1	0.488
- Phonophobia (%):	85	89.5	0.298
- Nausea (%):	67.3	72.4	0.392
- Vomitting (%):	30.6	30.5	0.982
- Osmophobia (%):	35.4	30.5	0.416
- Kinesiophobia (%):	76.2	74.3	0.729

Variable	Patients with BrS/DI-Type 1 BrP (n=156)	Control Group (n=112)	P-value
- Aura symptoms:			
- Visual aura (%):	56.1	32.4	2.0×10^{-4}
- Sensory aura (%):	36.7	27.6	0.129
- Retinal aura (%):	0.064	0	1.0
- Vestibular migraine (%):	14.9	2.9	0.002
- Familial migraine (%):	91	66.4	6.3×10^{-7}
- Number of first degree family members with migraine:	2 (Median-/Range 0 to 8)	1 (Median-/Range 0 to 9)	3.9×10^{-7}
- Induction of migraine headache during ACT (%):	7.9	0.9	0.010
- History of neurology consultation (%):	64.9	61	0.525
- History of neuroimaging (%):	50.7	49.5	0.857
Anti-Migraine Drugs			
- Ergot Alkaloids (%):	21.5	21.7	0.966
- Triptans (%):	10.7	8.5	0.552
- Tricyclic Antidepressants (%):	4.0	3.8	0.918
- Selective Serotonin Reuptake Inhibitors (%):	8.7	4.7	0.218
- Serotonin-Noradrenaline Reuptake Inhibitors (%):	4.0	2.8	0.617
- Anti-Epileptics (%):	5.3	0	0.022
- Flunarizine (%):	0.7	2.8	0.311
- Beta-Blockers (Metoprolol/Propranolol) (%):	2.7	0.9	0.406
- Nonsteroidal Anti-Inflammatory Drugs (%):	73.2	62.3	0.065
- Acetaminophen (%):	83.9	69.8	0.007

Data are given as mean ± SD, number of patients and percentages. ACT = Ajmaline challenge test, BrS = Brugada syndrome, DI-Type 1 BrP = Drug-Induced Type 1 Brugada ECG pattern, ICHD = International classification of headache disorders, VAS = Visual analog scale.

Table 2

Clinical Variables Predicting Underlying Brugada Syndrome/Drug-Induced Type 1 Brugada ECG Pattern Among Migraineurs

	Univariate Logistic Regression			Multivariable Logistic Regression			Stepwise Logistic Regression		
Variable	**OR**	**(95% CI)**	**P-value**	**OR**	**(95% CI)**	**P-value**	**OR**	**(95% CI)**	**P-value**
- Age-at-onset of migraine:	0.95	(0.92 – 0.98)	1.7×10^{-4}	0.98	(0.94 – 1.02)	0.229	0.95	(0.93 – 0.98)	0.004
- Pediatric migraine:	2.9	(1.7 – 5.0)	1.6×10^{-4}	1.7	(0.71 – 4.2)	0.229			
- Days with migraine/month:	1.05	(1.0 – 1.1)	0.019	1.05	(0.97 – 1.1)	0.215			
- Chronic migraine:	1.9	(1.1 – 3.6)	0.023	0.83	(0.27 – 2.6)	0.745			
- Visual aura:	2.7	(1.6 – 4.5)	2.3×10^{-4}	1.7	(0.92 – 3.1)	0.092	1.8	(1.0 – 3.4)	0.04
- Vestibular migraine:	5.8	(1.7 – 20.0)	0.005	5.1	(1.4 – 19.0)	0.015	5.4	(1.4 – 21.0)	0.013
- Familial migraine:	5.1	(2.6 – 10.0)	3.0×10^{-6}	3.8	(1.5 – 9.7)	0.004	4.4	(2.0 – 9.8)	1.3×10^{-4}
- Number of 1°family members with migraine:	1.5	(1.2 – 1.9)	2.0×10^{-4}	1.1	(0.8 – 1.4)	0.556			
- Induction of migraine headache during ACT:	9.4	(1.20 – 74.0)	0.033	9.1	(0.9 – 92.0)	0.061	9.0	(0.9 – 88.0)	0.058

ACT = Ajmaline challenge test, CI = Confidence interval, OR = Odds ratio.

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