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Increased prevalence of ECG suspicious for Brugada Syndrome in recent onset schizophrenia spectrum disorders

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ABSTRACT

Background: Schizophrenia is associated with an increased risk of sudden cardiac death, traditionally attributed to prolonged QTc interval and increased prevalence of cardiovascular risk factors. However, defective ion channels implicated in both schizophrenia and Brugada Syndrome (BrS) may be associated with an increased risk of cardiac arrhythmias. Moreover, these cardiac arrhythmias can be provoked by various drugs, including psychotropic drugs.
Objective: To assess the prevalence of the occurrence of ECG suspicious for BrS (suspect BrS-ECG) and the prevalence of BrS in patients with recent onset schizophrenia spectrum disorders (SSD).
Methods: In this case-control study, ECGs of 388 patients with recent onset SSD admitted between 2006 and 2015 and 844 healthy controls were made. All persons who had a suspect BrS-ECG were offered an ajmaline provocation test to diagnose or exclude BrS. Data on possible confounders were ascertained. Patients with and without suspect BrS-ECG were compared regarding clinical and ECG variables.
Results: Suspect BrS-ECG was found in 33 patients (8.5%) and 13 healthy controls (1.5%), with an adjusted Odds Ratio of 3.5 ($p < 0.0001$). This finding was not explained by potential confounders such as gender, age, ethnicity, cannabis use, cardiovascular risk factors, medication use or serum electrolytes. BrS was confirmed in three patients and one control.
Conclusion: A considerable subset of patients with recent onset SSD have suspect BrS-ECG, extending earlier findings in patients with chronic schizophrenia. Screening for BrS in schizophrenia could be relevant both to prevent sudden cardiac death and to identify a subgroup of patients with possible ion-channel dysfunctioning.

1. Introduction

Patients with schizophrenia have a 15–25 years shorter life expectancy compared to the general population, which is largely attributable to cardiovascular diseases with 30–50% of patients dying due to these diseases (Correll et al., 2015; Laursen et al., 2013; Ringen et al., 2014; Sweeting et al., 2013). This is partially explained by the 2 to 4 times increased risk of sudden cardiac death (SCD) (Correll et al., 2015). The increased risk of SCD is generally attributed to the abundance of cardiovascular risk factors in schizophrenia, such as metabolic disorders, dyslipidemia, diabetes, an unhealthy lifestyle as well as to QTc interval prolongation due to antipsychotics (Koponen et al., 2008). QTc interval prolongation can lead to a life-threatening ventricular arrhythmia, Torsades de Pointes (Koponen et al., 2008; Torniainen et al., 2015). However, it is difficult to ascertain that the excess mortality due to SCD can be fully explained by these factors (Kasper et al., 2010; Peuskens et al., 2007; Salvo et al., 2016).

Therefore, it is possible that other cardiac diseases are responsible for the increased risk of SCD. This is not unlikely, since several lines of research implicate aberrant ion channel function in a subgroup of patients with schizophrenia, which can increase the risk of cardiac arrhythmias as well (Cui et al., 2015; Dedic et al., 2018; Imbrici et al., 2013). Especially aberrant calcium function has been found in schizophrenia, both in large genome-wide association studies identifying several genes involved in voltage-gated calcium channel complexes as in a post-mortem gene expression study in brain tissue (Hertzberg et al., 2015; Pardinas et al., 2018; Ripke et al., 2013). Interestingly, similar genes have been implicated in a cardiac disease, called Brugada Syndrome (BrS) (Berne and Brugada, 2012).

BrS can provoke lethal cardiac arrhythmias and has been estimated to cause 4% of all sudden cardiac deaths (SCD) in the population and at least 20% of SCD in people without structural heart disease (Berne and Brugada, 2012). Risk of future SCD depends on several parameters, where patients at high risk receive a prophylactic implantable cardioverter-defibrillator (Berne and Brugada, 2012). Cardiac ion

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channel dysfunction plays a major role in the pathogenesis of BrS (Sieira et al., 2016). BrS generally manifests itself more often in males and around the age of 40 (with a large variance). It is a rare disease with an estimated prevalence of 1 to 5 in 10,000 persons, except in South-East Asia where a higher prevalence of 12 to 15 in 10,000 has been reported (Berne and Brugada, 2012; Matsuo et al., 2001; Miyasaka et al., 2001; Sieira et al., 2016). The disease is hereditary in about 50% of patients. At present, mutations in 22 genes encoding subunits of several ion channels (sodium, potassium and calcium) have been identified (Berne and Brugada, 2012; Sieira et al., 2016). Mutations are most commonly found in the voltage dependent sodium channel gene SCN5A (20–30% of patients) (Arbelo and Brugada, 2014). Several pathophysiological mechanisms for the ion channel dysfunctions have been proposed, including acquired causes of cardiac dysfunction such as epicardial fibrosis (Sieira et al., 2016).

BrS is diagnosed by specific alterations found on the ECG, whereby these alterations have been characterized as either diagnostic for BrS (Type 1 pattern) or as possibly indicating BrS (Type 2 or 3 pattern, henceforward called suspect BrS-ECG, see Fig. 1) (Berne and Brugada, 2012; Sheikh and Ranjan, 2014; Wilde et al., 2002). Notably, the ECG pattern of patients with BrS is known to change over time, changing from perfectly normal or suspect BrS-ECG to type 1 BrS-ECG (Arbelo and Brugada, 2014). Therefore, when a suspect BrS-ECG is found, additional testing is needed to confirm or reject BrS. This can be done by intravenous administration of a cardiac sodium channel blocking drug (e.g., ajmaline) (Tadros et al., 2017). If the ECG changes to a Type 1 BrS-ECG, BrS is confirmed (Berne and Brugada, 2012).

Our previous study has shown an increased prevalence of suspect BrS-ECG in patients with chronic schizophrenia compared to two control cohorts (11.6% vs. 1.1% and 2.4%, respectively) (Blom et al., 2014), lending support to the hypothesis that a common pathophysiological mechanism underlying both BrS and schizophrenia could be involved (Liao and Soong, 2010). However, in patients with chronic schizophrenia (cardiovascular) comorbidities are already highly prevalent, which leaves uncertainty about the validity of these findings. The assessment of suspect BrS-ECG in patients with recent onset schizophrenia compared to controls would less likely be confounded by comorbidities in this relatively young patient group.

1.1. Aims of the study

We set out to determine whether suspect BrS-ECG is more prevalent in patients with recent onset schizophrenia spectrum disorders (SSD) compared to healthy controls. Secondly, we wanted to ascertain whether any covariates influenced the risk of having a suspect BrS-ECG in patients with recent onset SSD. Lastly, we studied differences in clinical and ECG parameters within the group of patients with and without suspect BrS-ECG.

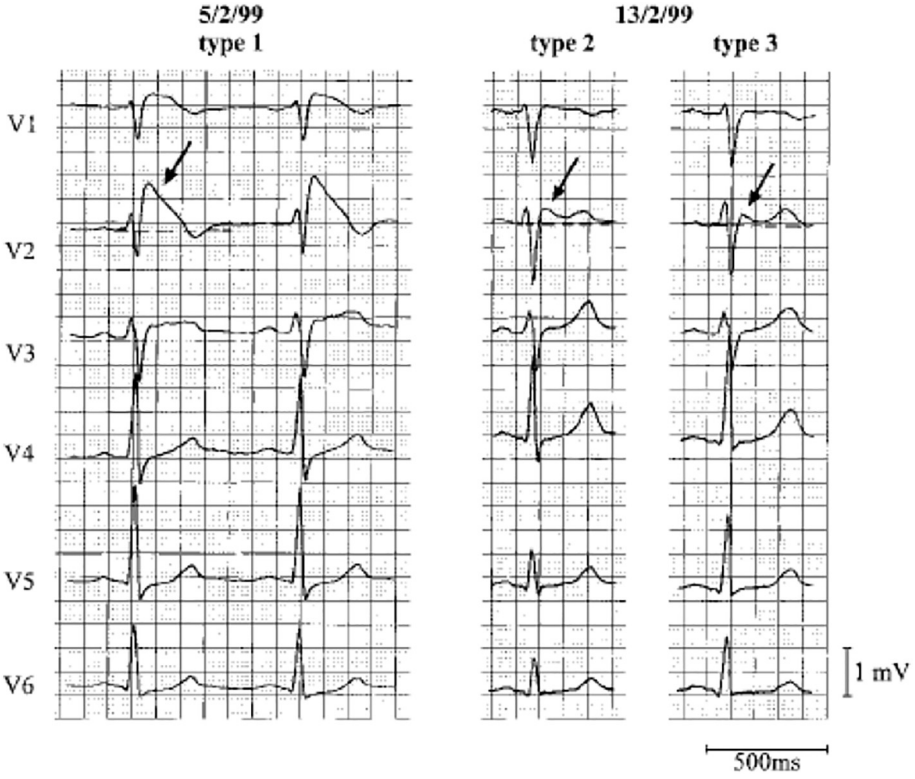

Fig. 1. Precordial leads of resuscitated patient with Brugada Syndrome with dynamic ECG changes in the course of a few days. All three BrS ECG-patterns are shown. ST-segment abnormalities can be seen in leads V_1 to V_3:

	Type 1	Type 2	Type 3
J wave amplitude	≥2 mm	≥2 mm	≥2 mm
T wave	negative	positive or biphasic	positive
ST-T configuration	coved type	saddleback	saddleback
ST segment (terminal	gradually descending	elevated ≥1 mm	elevated <1 mm

1 mm=0.1 mV. The terminal portion of the ST segment refers to the latter half of the ST segment.

Figure copied with permission from: De Wilde AM, Antzelevitch C, Borggrefe M, et al. Proposed Diagnostic Criteria for Brugada Syndrome. Consensus report. Circulation 2002 Nov 5;106 (19):2514–9 (20).

2. Materials and methods

2.1. Case cohort

In this case-control study, cases were drawn from the group of patients with recent onset psychosis and a DSM-IV diagnosis of a schizophrenia spectrum disorder that had been hospitalized at the Early Onset Psychosis Department of the AMC, an academic hospital, between January 2006 and November 2015. Generally, these patients are first episode psychosis patients who are treated in our Early Psychosis Department often within the first year of treatment. Patients with a treatment duration of over five years are no longer considered to be eligible for treatment in our department. In all such patients, a routine ECG is performed to exclude cardiac disorders. Patients with a suspect BrS-ECG were asked to undergo further investigations in order to ascertain whether BrS was present or not. This included performing a specific ECG recording, with placement of parasternal ECG leads in more cranial positions (second instead of fourth intercostal spaces) in order to increase the sensitivity for detecting BrS-ECG (Meregalli et al., 2005). Patients with a suspect BrS-ECG were subsequently seen by a cardiologist (HLT) and provocation testing with intravenous ajmaline was advised. When provocation testing confirmed BrS, the SCN5A gene - the gene most commonly associated with BrS (in 20–25% of all cases) (Berne and Brugada, 2012) - was tested for mutations. Patients also completed a questionnaire about (psychiatric and somatic) comorbidities, medication use and risk factors for cardiovascular disease.

2.2. Control cohort

Between 2013 and 2015 medical students recorded ECGs of each other during their second-year cardiology course for educational purposes. ECGs of students who were willing to participate in the study (controls) were collected and analyzed. All controls completed a questionnaire asking for gender, age, height and weight, psychiatric disorders, family history of psychiatric disorders and for current medication use. Informed consent was asked to use this data anonymously for this study. Controls with a suspect BrS-ECG were asked to undergo the same diagnostic procedures as patients in order to ascertain whether BrS was present or not.

Students were excluded when questionnaires were returned without name and/or signature, when suffering from any psychiatric disorder, when having a (first-degree) family history of schizophrenia or schizophrenia spectrum disorders and when using any psychotropic medication.

2.3. Clinical variables

In patients, information on demographics, diagnoses, comorbidities, laboratory results, medication and substance use at the moment of ECG recording and risk factors for cardiovascular disease were obtained by analysis of medical records. In patients using antipsychotics, a therapeutic equivalence dose (chlorpromazine equivalent, CPE) was calculated using the International Consensus Study of Antipsychotic Dosing (Fabbri et al., 2017). Use of concomitant medication was noted. To determine which medication was associated with the potential to elicit (suspect) BrS-ECG, www.brugadadrugs.org was accessed (depolarization-blocking drugs) (Postema et al., 2009); to determine which medication was associated with QT-interval prolongation, the AZ-cert list was consulted (QT-prolonging drugs) (Boerman et al., 2016). In students, information on demographics, medication and substance use was obtained from the questionnaire. Laboratory test were not performed.

2.4. ECG analysis

All ECGs were analyzed by a cardiologist at the AMC, specialized in cardiac arrhythmias, sudden cardiac death and BrS (HLT). BrS-ECGs were categorized as type 1 or suspect BrS-ECG (Berne and Brugada, 2012). The QTc duration was measured by the cardiologist and heart rate-corrected (Bazett formula). In all students with a suspect BrS-ECG, ECG recording was repeated in order to rule out technical problems or incorrect ECG lead placement during the course. All students whose second ECG still showed a suspect BrS-ECG were advised to consult a cardiologist. When ECG recording had been repeated, the classification of the second ECG was used for statistical analysis.

2.5. Statistical analysis

To analyze differences in age, gender and medication use between patients and controls, we used $\chi 2$ statistics (Pearson/Fisher exact where appropriate) for categorical variables and *t*-test for continuous variables. Difference in BMI and ECG parameters were analyzed using regression analysis while correcting for age and sex, to account for differences in age and especially sex distribution between cohorts. We then performed multivariate logistic regression analyses to assess differences between patients and controls in suspect BrS-ECG prevalence, correcting for variables that were significantly ($p < 0.05$) different between cohorts, but not for medication use since controls did not use QT-prolonging or depolarization-blocking drugs. Next, we compared medication use, comorbidities and ECG parameters between patients with or without suspect BrS-ECG, using $\chi 2$ statistics (Pearson/Fisher exact where appropriate) for categorical variables. For continuous variables, *t*-test was used when normally distributed and Mann-Whitney *U* when not-normally distributed to calculate the p-value. Difference in QTc-duration was assessed using logistic regression analysis correcting for sex, since QTc-durations are sex-dependent.

A p-value of <0.05 was considered statistically significant. All statistics were performed in SPSS (version 20.0 for Mac, Chicago, IL).

3. Results

After exclusion of 43 controls and 23 patients following our predetermined criteria, the database consisted of 388 patients and 844 controls (Fig. 2, Table 1). Patients were slightly, but statistically significantly, older (age 22 vs. 20 years, $p < 0.001$), and were more often men (82% vs. 35%, $p < 0.001$). Also, patients had a higher BMI (24.1 vs. 21.8, $p < 0.001$). None of the controls used QT-prolonging or depolarization-blocking drugs, whereas the majority of patients used QT-prolonging drugs (80.6%) and a smaller proportion used depolarization-blocking drugs, which could theoretically induce suspect BrS-ECG (5.4%).

Patients exhibited significantly more often suspect BrS-ECG than controls (8.5% vs. 1.5%, $p < 0.001$). Also, patients had higher heart rates (75.9 vs. 69.5 beats/min), shorter QRS-intervals (94.5 vs. 96.8 ms), shorter PR-intervals (144.2 vs. 150.1 ms; all differences statistically significant). Overall, QTc-durations were similar between patients and controls (387.4 vs. 387.7); however, when corrected for sex a statistically significant difference was observed ($p = 0.002$).

All patients ($n = 33$) and controls ($n = 13$) that showed suspect BrS-ECG were invited for a follow-up consult with a cardiologist. Among patients, 28 (85%) visited the cardiologist, of whom 22 (79%) agreed to undergo ajmaline testing, yielding three positive tests. Among controls, 12 (92%) visited the cardiologist, of whom 8 (62%) agreed to undergo ajmaline testing, yielding one positive test. Thus, the proportion of positive tests was similar for both groups (14% and 13%, respectively).

Table 2 shows associations between presence/absence of schizophrenia and suspect BrS-ECG. When adjusted for characteristics that were univariately associated with suspect BrS-ECG (male sex and age), schizophrenia was associated with a more than three-fold increased risk of suspect BrS-ECG (OR_{adj} 3.5, $p = 0.001$). There were no statistically significant interactions of this association with age or sex.

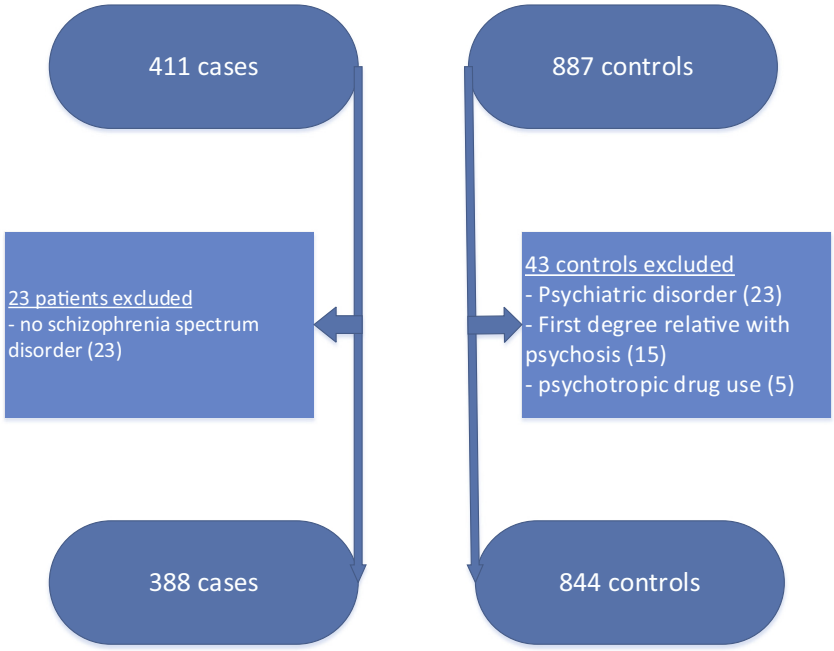

Fig. 2. Flowchart selection of cases and controls following in- and exclusion criteria.

In order to assess whether clinical variables might influence the occurrence of suspect BrS-ECG among patients, we compared demographics, comorbidities, medication use and ECG parameters among patients with or without suspect BrS-ECG (Table 3). There were no statistically significant differences between both groups, except for the ECG parameters: patients with suspect BrS-ECG (n = 33) had lower heart rates (p = 0.014), longer QRS-duration (p = 0.002) and shorter QTc-durations (p = 0.025) than patients without suspect BrS-ECG (n = 355).

We further mention a trend towards a higher percentage of male sex in patients with suspect BrS-ECG (93.9% vs. 80.8%, p = 0.061) and higher use of first-generation antipsychotic medication (24.2% vs. 13.0%, p = 0.076). Haloperidol was the most commonly used first-generation antipsychotic (24.2% vs. 10.8%, p = 0.022, data not shown). Remarkably, none of the patients with suspect BrS-ECG used Brugada drugs.

Table 1
Characteristics of patients and controls.

	Patients	Controls	p-Value[a]	Missing
	n = 388	n = 844		
Demographics				
Male sex, n (%)	318 (82.0)	298 (35.3)	<0.001	
Mean age, years (SD)	22.4 (3.6)	20.4 (1.5)	<0.001	3
Diagnosis				
Schizophrenia, n (%)	275 (70.9)	–		
Schizoaffective disorder, n (%)	56 (14.4)	–		
Schizophreniform disorder, n (%)	24 (6.2)	–		
Psychosis due to cannabis use, n (%)	4 (1.0)	–		
Psychosis NOS, n (%)	29 (7.5)	–		
Comorbidities				
Current use of cannabis, n (%)	27 (7.0)			78 (20.1)
Mean BMI kg/m^2 (SD)	24.1 (4.4)	21.8 (2.7)	<0.001	159 (12.9)
Medication use				
Antipsychotics, n (%)	350 (90.2)	0	<0.001	2 (0.2)
Antidepressants, n (%)	28 (7.2)	0	<0.001	2 (0.2)
QT-prolonging drugs, n (%)	311 (80.6)	0	<0.001	2 (0.2)
Depolarization blocking drugs, n (%)	21 (5.4)	0	<0.001	2 (0.2)
ECG parameters				
Suspect BrS-ECG, n (%)	33 (8.5)	13 (1.5)	0.001	2 (0.2)
Mean heart rate, beats/min (SD)	75.9 (15.7)	69.5 (12.3)	<0.001	1 (0.1)
Mean QRS-duration, ms (SD)	94.5 (10.6)	96.8 (12.4)	<0.001	1 (0.1)
Mean PR-interval, ms (SD)	144.2 (19.4)	150.1 (20.6)	<0.001	17 (1.4)
Mean QTc-interval, ms (SD)	387.4 (28.1)	387.7 (26.2)	0.004	

SD = standard deviation; BMI = body mass index; ECG = electrocardiogram; ms = millisecond.

[a] For categorical variables the p-value was calculated with Chi-square test or Fisher's exact test where appropriate. In case of continuous variables, the p-value was calculated using regression analysis corrected for age and sex.

4. Discussion

Our study shows that patients with recent onset schizophrenia have a significantly increased risk of having a suspect BrS-ECG, confirming and extending earlier findings in a population with chronic schizophrenia (Blom et al., 2014). Since patients with recent onset schizophrenia have a much lower risk of (cardiovascular) comorbidities, limiting the risk of confounding, this could point to a common etiological background. Moreover, additional analysis shows that the patients with suspect BrS-ECG do not differ from patients without suspect BrS-ECG regarding metabolic factors, cannabis abuse or type of medication use. Specifically, patients with suspect BrS-ECG did not use depolarization-blocking drugs more often than patients without, which makes it unlikely that this finding can be explained by these confounding factors.

So far, studies on ECG recordings in schizophrenia patients have mainly focused on the increased prevalence of QTc prolongation, which was found in our study as well and has been associated with the use of antipsychotic drugs (Nielsen et al., 2011; van Noord et al., 2009). The finding of increased prevalence of suspect BrS-ECG is new and deserves further attention since it could be a reflection of an inherited ion channel dysfunction, thus pointing to a possibly distinct biotype in schizophrenia. More research is clearly necessary, but several lines of evidence already support such a hypothesis. Firstly, genetic data point to in the involvement of calcium channel subunits as a player in the pathophysiology for a subgroup of patients with schizophrenia (and bipolar disorder) (Dedic et al., 2018; Jiang et al., 2015; Marshall

Table 2
Association of schizophrenia spectrum disorders with suspect Brugada ECG pattern.

	Suspect BrS-ECG	No suspect BrS-ECG	OR (95% CI)	p-Value	OR_{adj} (95% CI)[a]	p-Value
	n = 46	n = 1184				
Schizophrenia spectrum disorders, n (%)	33 (71.7)	355 (30.0)	5.9 (3.1–11.4)	<0.001	3.5 (1.7–7.2)	0.001
Male sex, n (%)	40 (87.0)	574 (12.4)	7.09 (3.0–16.8)	<0.001	4.0 (1.6–10.1)	0.003
Mean age, years (SD)	22.0 (3.2)	21.0 (2.5)	1.12 (1.03–1.23)	0.013	1.00 (0.91–1.11)	0.956
Mean BMI, kg/m^2 (SD)	22.5 (2.0)	22.4 (3.4)	1.01 (0.92–1.11)	0.814		

ECG = electrocardiogram; BMI = body mass index; OR = odds ratio; OR_{adj} = adjusted odds ratio, CI = confidence interval.
There was no significant interaction between sex and schizophrenia (p = 0.879) or between age and schizophrenia (p = 0.334).
[a] Adjusted for male sex and age.

et al., 2017). Secondly, several studies investigating the effect of calcium ion channel modulation show that aberrant CACNA1C expression before adulthood influences brain maturation and could lead to cognitive decline, impaired synaptic plasticity, reduced sociability, hyperactivity and increased anxiety (Dedic et al., 2018).

Moreover, the shorter QTc duration with suspect BrS-ECG in schizophrenia patients is remarkable. ECGs of BrS patients usually show a normal QTc interval (Postema et al., 2010), but a subtype of BrS with short QTc intervals has been described, which is related specifically to aberrant calcium channel functioning (Le Scouarnec et al., 2015). Nevertheless, we did not test specific calcium ion channel gene mutations in the schizophrenia patients with BrS-ECG to investigate this. We did identify one patient with BrS, whereby the mother had BrS (but no psychiatric disorder) as well, indicating a genetic component.

Alternative explanations for this association should be considered as well, especially factors increasing both the risk of developing a psychosis as well as suspect BrS-ECG. As mentioned earlier, a variety of psychotropic drugs impact on ion channel functioning, including drugs which block depolarizing ion channels (e.g. the sodium channel). Also, cannabis intoxication can alter ECG conduction through modifying ion channel functioning (Daccarett et al., 2007). In our study, we did not find an indication that our results are influenced by the use of cannabis or agents with sodium channel blocking properties such as antidepressants and lithium. However, we did find a modest increased use of haloperidol in patients with suspect BrS-ECG, but this alone cannot explain the increased prevalence of suspect BrS-ECG in schizophrenia patients. Finally, it has been shown that vitamin D deficiency at critical time points can permanently alter L-type calcium channels function during

Table 3
Characteristics of patients with schizophrenia spectrum disorders according to Brugada ECG pattern. Significant p-values are shown in bold.

	Suspect BrS-ECG	No suspect BrS-ECG	p-Value	Missing
	n = 33	n = 355		
Demographics				
Male sex	31 (93.9)	287 (80.8)	0.061	–
Mean age, years (SD)	22.7 (3.4)	22.4 (3.6)	0.630	–
Caucasian	17 (53.1)	156 (47.6)	0.548	28 (7.2)
Diagnosis				
Schizophrenia	22 (66.7)	253 (71.3)	0.897	
Schizoaffective disorder	6 (18.2)	50 (14.1)		
Schizophreniform disorder	4 (12.1)	20 (5.6)		
Psychotic disorder due to cannabis	0 (0)	4 (1.1)		
Psychotic disorder NOS	1 (3.0)	28 (7.9)		
Comorbidities				
Mean BMI, kg/m^2 (SD)	22.7 (2.1)	24.3 (4.6)	0.090	146 (37.2)
Mean waist circumference, cm (SD)	83.6 (8.5)	88.6 (12.8)	0.082	198 (51.0)
Current use of cannabis	3 (10.0)	24 (8.6)	0.735	78 (20.1)
Median total cholesterol/HDL ratio (IQR)	3.1 (1.3)	3.4 (1.7)	0.258	26 (6.7)
Mean serum sodium level, mmol/l (SD)	142.0 (2.0)	141.5 (1.9)	0.184	7 (1.8)
Mean serum potassium level, mmol/l (SD)	4.0 (0.3)	4.1 (0.3)	0.792	6 (1.5)
Medication use				
Antipsychotics	31 (93.9)	319 (90.4)	0.755	2 (0.5)
FGAs	8 (24.2)	46 (13.0)	0.076	2 (0.5)
SGAs	24 (72.7)	279 (79.0)	0.339	2 (0.5)
Median CPE (IQR)	300.0 (280.0)	320.0 (280.0)	0.831	11 (2.8)
Antidepressants	2 (6.1)	26 (7.4)	1.000	2 (0.5)
SSRIs	2 (6.1)	24 (6.8)	1.000	2 (0.5)
TCAs	0 (0)	2 (0.6)	1.000	2 (0.5)
Lithium	0 (0)	10 (2.8)	1.000	2 (0.5)
Benzodiazepines	18 (54.6)	211 (59.9)	0.577	3 (0.8)
QT-prolonging medication	29 (87.9)	282 (79.9)	0.359	2 (0.5)
Depolarization blocking drugs	0 (0.0)	21 (5.9)	0.239	2 (0.5)
ECG parameters[a]				
Mean heart rate, beats/min (SD)	69.6 (12.2)	76.5 (15.8)	**0.020**	–
Mean QRS-duration, ms (SD)	100.0 (9.8)	94.0 (10.5)	**0.012**	–
Mean PR-interval, ms (SD)	144.1 (15.9)	144.2 (19.7)	0.997	3 (0.8)
Mean QTc-interval, ms (SD)	375.9 (33.4)	388.5 (27.4)	**0.025**	1 (0.3)

All numbers are n (%), unless otherwise indicated. SD = standard deviation; BMI = body mass index; HDL = high-density lipoprotein; IQR = interquartile range; FGAs = first-generation antipsychotics; SGA = second-generation antipsychotics; CPE = chlorpromazine equivalent.
p-Value was calculated using chi square for categorical variables. For continuous variables, *t*-test was used when normally distributed and Mann-Whitney *U* when not-normally distributed.
[a] p-Values of ECG parameters were calculated with regression analysis and corrected for sex.

development, impacting brain function in mice (Cui et al., 2015). Vitamin D deficiency has been found in patients with schizophrenia (Boerman et al., 2016; Chiang et al., 2016; Cui et al., 2015), but a relation with suspect BrS-ECG has so far not been reported. Since we did not measure vitamin D levels in our patients or controls, this factor cannot be ruled out.

In accordance with earlier findings, we found an increased prevalence of suspect BrS-ECG in males (Sheikh and Ranjan, 2014). After correction for sex, the increased prevalence was still significantly higher. Also, a post hoc analysis evaluating only males in both groups yielded a similar significant odds ratio (OR 3.6, $p = 0.002$). In schizophrenia, male preponderance is well-known (Sutterland et al., 2013), just as in BrS (Berne and Brugada, 2012).

Apart from the biotype hypothesis, discovering BrS in schizophrenia remains a clinically relevant finding on its own, since it has important consequences in prescription choices and lifestyle advices. Factors that are known to provoke potentially lethal arrhythmias in BrS are cannabis and cocaine intoxication, hypo- and hyperkalaemia, fever, but also certain drugs acting on ion channels including commonly prescribed psychotropic drugs: antidepressants, beta blockers and lithium (Arbelo and Brugada, 2014; Sicouri and Antzelevitch, 2008). Therefore, when BrS is identified in patients with schizophrenia, some psychotropic drugs need to be avoided or alternatives need to be prescribed in order to prevent SCD. For a complete list of drugs to be avoided in BrS, we refer to the regularly updated website www.brugadadrugs.org (Postema et al., 2009).

Taken together, screening for BrS-ECG in schizophrenia could potentially be relevant to both prevent SCD as well as to identify a subgroup of patient with aberrant ion channel functioning.

4.1. Strengths and limitations

Our study has several strengths. First of all, in our study we included a substantial group of patients with recent onset schizophrenia spectrum disorders, rendering the chance of bias due to acquired (cardiovascular) diseases that could influence ECG abnormalities to be small. Moreover, we were able to study the influence of possible confounders. Furthermore, we could compare SSD patients with a healthy control group of similar age, making it the first true case control study investigating the prevalence of (suspect) BrS-ECG.

However, we need to acknowledge several limitations of our study as well. First of all, in our healthy control group of medical students, 65% was female, whereas in our case cohort, the majority of patients were male (82%). Also, the healthy controls were slightly but significantly younger. We addressed this gender and age difference in our analysis by adjusting for age and gender and by analyzing male patients and controls separately while adjusting for age. Secondly, ECG analysis by the cardiologist was not blind for cohort status. Nevertheless, strict criteria for diagnosing BrS-ECG patterns have been formulated (Hall et al., 2015), which were rigorously followed, rendering the chance of bias small. Thirdly, after ajmaline testing, just three patients with confirmed BrS were found among patients with schizophrenia spectrum disorders. Therefore, it remains uncertain whether BrS as cardiac disease itself is more prevalent in patients with SSD, or only an ECG pattern that is suggestive of BrS. Still, the estimated prevalence of BrS in the general population was reported to be much lower than the prevalence found in our case cohort. Also, the proportion of positive ajmaline tests was equally high among patients and controls that underwent this test. Finally, patients that had been tested positive for BrS suspect ECG did not undergo testing of ion channel-encoding genes such as CACNA1C. This leaves uncertainty on the connection between the ECG findings and ion channel dysfunctioning.

4.2. Future directions

While the current findings are important with regard to both clinical consequences and biomarker discovery, more research is warranted to validate these findings. Considering clinical consequences, the increased prevalence of suspect BrS-ECG should be replicated in other studies. If indeed a similar proportion would be found, follow-up studies are necessary to investigate whether an increased incidence of SCD is associated with suspect BrS-ECG at baseline. Furthermore, future studies could evaluate whether patients with suspect BrS-ECG show differences in symptom severity or clinical course of psychosis.

With respect to biomarker discovery, investigating whether ion channel dysfunctioning is more present in schizophrenia patients with suspect BrS-ECG is an important step. This could be done by studying genetic mutations/variations in a larger patient sample or studying aspects of brain functioning in animal models of BrS. Also, investigating whether this increased prevalence of suspect BrS-ECG in patients with schizophrenia spectrum disorders is in some way related to vitamin D deficiency now or during development could be valuable.

In summary, our study shows that patients with recent onset schizophrenia have an increased risk of having a suspect BrS-ECG, confirming and extending earlier findings. Screening for BrS in schizophrenia could both be relevant to prevent sudden cardiac death as well as to identify a subgroup of patients with possible ion channel dysfunctioning.

Contributors

Authors AS, MB, LdH and HLT designed the study and wrote the protocol. Author AS and KL recruited patients for Brugada screening. Author KL, JJL and MB recruited and tested healthy controls. Authors HLT performed Brugada screening and additional provocation test if necessary. Authors MB, KL and AS undertook the statistical analysis and author AS and MB wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

All authors declare no conflict of interest.

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