The type 1 coved ST-segment Brugada ECG pattern is said to be unusual in a general population, perhaps occurring in 0.1% of European descent populations, and possibly more often, ≤0.2%, in East Asians. Therefore, it is surprising that in this issue of *Circulation: Arrhythmia and Electrophysiology*, Blom et al report identifying a Brugada ECG pattern in 11.6% (32/275) of patients with schizophrenia. The finding is unexpected and may carry interesting implications both for mechanisms and for patient care.

Could This Be a False-Positive Result?

Only 1 subject had the definitive type 1 ECG pattern, and the other 31 had the less specific type 2 to 3 pattern, whose frequency in the general population has not been well established. The authors did examine the prevalence of the Brugada ECG pattern in 2 control groups. In a small group of young healthy population controls, the type 2 to 3 pattern was seen in 2/179 (1.1%) subjects, whereas in a group of older population controls, the prevalence was 28/1168 (2.4%). In the present study, 23 of the 31 patients with the type 2 to 3 pattern consented to provocative testing with ajmaline and 10/23 then displayed the type 1 pattern. Although there was no family or personal history of syncope or cardiac arrest, this finding adds weight to the conclusion that the high prevalence of the pattern seems to be a real finding. There was no type 1 ECG in either control group, and for study design reasons the controls were not accessible for ajmaline testing. Importantly, all the ECGs were analyzed by a single adjudicator, blind to case/control status.

One obvious potential confounder is that the patients may have been receiving drugs that provoked or exacerbated the Brugada ECG pattern. This is well recognized with antidepressants and other psychoactive drugs and is thought to reflect these agents’ sodium channel blocking properties. However, in the 198 subjects with schizophrenia not receiving sodium channel blocking drugs, the prevalence of the pattern remained high (19/198). Variations in autonomic function, specifically enhanced vagal activity or inhibited sympathetic activity, can provoke the Brugada ECG pattern, but this seems unlikely here: schizophrenics generally display decreased heart rate variability and the mean heart rate in the schizophrenic subjects studied here was in fact higher than that in controls. It remains formally possible that the ECG effect reflects some heretofore unappreciated class effect of antischizophrenic drugs, perhaps not acting on sodium channels (eg, enhancing the transient outward current or decreasing L-type calcium current). However, taken together, it is hard to argue that the findings reported here represent a false-positive.

Schizophrenia and Sudden Cardiac Death

The authors’ stated rationale for undertaking this study in the first place was to search for ECG markers of a well-recognized increased risk for sudden cardiac death (SCD) in schizophrenia. For example, using Medicaid databases, Hennessy et al estimated that schizophrenics had a 1.7- to 3.2-fold increased risk for SCD. Ray et al reported similar increases in risk for users of both first-generation and second-generation (atypical) antipsychotics.

Three factors have been invoked to explain this increased frequency of SCD: a much higher prevalence of risk factors for coronary artery disease, the autonomic dysfunction mentioned above, and QT-interval prolongation because of the use of cardioactive psychotropic drugs. As is well-recognized in the literature, and mirrored in the present study, there is an increased prevalence of diabetes mellitus, obesity, hypercholesterolemia, sedentary habits, and tobacco use in schizophrenia, and these presumably account for an increased incidence of manifest coronary disease and likely SCD. Antipsychotic drugs, such as thioridazine and haloperidol, were among the earliest noncardiovascular drugs to be implicated in drug-induced torsades de pointes, and thus undoubtedly contribute to some extent to the increased incidence of SCD. However, although the extent to which contemporary psychotropic pharmacotherapy increases QT-interval prolongation is well-characterized, and less than that seen with thioridazine, the extent to which these generally modest increases in QT contribute to the overall recognized increased SCD risk in schizophrenia is not known.

The authors of the present study also reported that QTc intervals were longer in schizophrenics than in controls. Interestingly, they found that this difference disappeared after correction for covariates known to affect QT, such as diabetes mellitus and medication use; as noted above, the analysis presented here suggests that the Brugada syndrome pattern persists even after correction for the use of sodium channel blocking drugs. Thus, although QT-interval prolongation in schizophrenia may reflect comorbidities, the Brugada pattern appears at this point independent at least of concomitant medications. The extent to which either ECG marker contributes to SCD risk remains unknown, but it seems difficult to argue that they play absolutely no role.
Genetics and the Brugada ECG

One possible explanation for the finding here is that the less specific type 2 to 3 ECG pattern is actually much commoner than appreciated in the general population. The findings in the relatively small control groups studied here argue against this conclusion, but a recent survey reported the type 2 to 3 ECG pattern in 11.8% of male athletes and 9.9% of population controls, when V1 and V2 were recorded using the second intercostal space.16 Another recent study highlighted the frequency (∼2%) with which the type 1 Brugada ECG pattern was seen in febrile patients in an emergency room setting,17 again suggesting that the asymptomatic syndrome is commoner than previously appreciated.

After 2 decades of intensive clinical and molecular genetics, a causative rare variant can now be identified in the majority of patients with long-QT syndrome or arrhythmogenic cardiomyopathy but in the case of the Brugada syndrome (let alone simply the ECG pattern), the proportion remains much smaller. Indeed, debate persists about the fundamental functional and molecular lesion(s) in this entity, how often multiple gene variants are required to elicit the phenotype,18 and the extent to which manifest or subclinical structural heart disease contributes.19 Only 1 of the patients with the Brugada ECG harbored a rare SCN5A variant, c.3956G>T resulting in G1319V, previously reported in Brugada syndrome and characterized as a reduction of function allele,20 and also observed in 1/2100 black subjects (http://evs.gs.washington.edu/EVS/).

What Next?

The present study suggests that the type 2 to 3 Brugada ECG is unusually prevalent in schizophrenia, but additional work both in schizophrenia and in the general population is needed to put this finding in context: as discussed above, the frequency of this pattern is not well established in the general population. If, indeed, it turns out to be more prevalent in schizophrenia, the underlying mechanism for the link would certainly be worth exploring. Does this represent more general manifestations of the increasingly well-appreciated link between central nervous system disease and arrhythmia susceptibility21 Or some common genetic or epigenetic mechanisms?22 Or some undescribed drug effect?

It is further tantalizing to suggest that the Brugada mechanism contributes to an unusually high incidence of SCD in schizophrenia, but the extent of that contribution remains uncertain. Although electrocardiographic screening to identify patients with the pattern predrug, or on-drug, seems reasonable, the burden of this intervention would be considerable, and how identifying a patient with a type 2 to 3 pattern might translate into a clinical recommendation remains uncertain. Reasonable next steps in unraveling this story are to validate the finding in larger case and control populations, to explore possible mechanisms further, and to establish a relationship if any between these ECG changes and SCD before considering screening ECGs as a routine.

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