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CASE REPORT

Paradoxical effect of ajmaline in a patient with Brugada syndrome

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Aims The typical Brugada ECG pattern consists of a prominent J-wave associated with ST-segment elevation localized in the right precordial leads V1–V3. In many patients, the ECG presents periods of transient normalization and the Brugada-phenotype can be unmasked by the administration of class-I antiarrhythmics. Reports have documented the heterogeneity of the Brugada syndrome ECG-phenotype characterized by unusual localization of the ECG abnormalities in the inferior leads.
Case report A 51-year-old man, without detectable structural heart disease, was referred to us because of a history of syncope, dizziness, and palpitations. The ECG showed a J-wave and ST-segment elevation in the right precordial leads, suggesting Brugada syndrome. As other causes of the ECG abnormalities were excluded, the patient underwent an electrophysiological study that documented easy induction of ventricular fibrillation. During infusion of ajmaline, new prominent J-waves and ST-segment elevation appeared in the inferior leads, whereas the basal ECG abnormalities in the right precordial leads normalized. After infusion of isoprenaline, the ECG-pattern resumed the typical Brugada pattern. An implantable cardioverter-defibrillator was recommended.
Conclusion In our patient, the double localization of the typical Brugada-pattern and the paradoxical effect of ajmaline on the ECG abnormalities confirmed the possibility of a phenotype heterogeneity in the Brugada syndrome.

Introduction

Brugada syndrome[1] is a hereditary arrhythmogenic disease, with autosomic transmission, characterized by a propensity for life-threatening ventricular arrhythmias in the absence of structural cardiac disease.[2,3] The diagnosis is based on the presence of typical surface ECG alterations characterized by a prominent J-wave in V1–V3 associated with an rSr′ pattern mimicking right bundle branch block.[4] However, in many individuals with Brugada syndrome, the appearance of a typical ECG phenotype may be intermittent: in such cases, the ECG abnormalities can be unmasked by the administration of class-I antiarrhythmics.[5,6]

We describe a case of paradoxical effects of drug-challenge with ajmaline in a patient with Brugada syndrome with double localization, anterior and inferior wall, of the typical pattern of ECG abnormalities.

Case report

A 51-year-old man with mild hypertension on treatment with angiotensin-converting enzyme-inhibitors and diuretics was referred to our cardiology department because of dizziness associated with brief palpitations. There was no family history of sudden death, but 11 years earlier the patient had syncope, without prodrome, while driving a car. On that occasion, the cause was ascribed to a not previously known small subarachnoid cyst, seen on cranial CT scan, and surgically removed. The patient had no preceding history of epilepsy or abnormal EEG. Physical examination, laboratory analysis, and chest X-rays were normal. The 12-lead ECG showed sinus rhythm with normal PQ, QRS, and corrected QT intervals; a slight 'coved-type' ST-segment elevation associated with rSr′ pattern was noted in V1, and a 'saddle-back type' ST in V2 and V3 (*Figure 1*). Echocardiography showed normal cardiac structure and no thoracic abnormalities on magnetic resonance imaging. Holter monitoring registered a total of 1543 premature ventricular, polymorphic, non-repetitive complexes (PVCs) and the heart-rate-variability parameters were normal (SDNN = 120.3 ms, ASDNN 5 = 69.4 ms, SDANN 5 = 93.1 ms). The signal-averaged ECG did not show late ventricular potentials. Exercise stress testing was negative for induction of either transient acute myocardial ischaemia or arrhythmias.

The patient was taken to our electrophysiological (EP) laboratory with a diagnosis of Brugada syndrome. The EP

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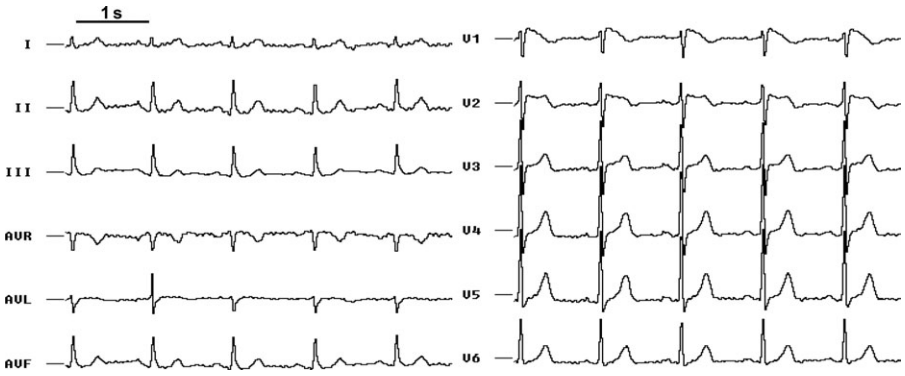

Figure 1 12-lead ECG on admission. Typical ECG abnormalities of Brugada syndrome are evident in V1–V3, the tracing being otherwise normal.

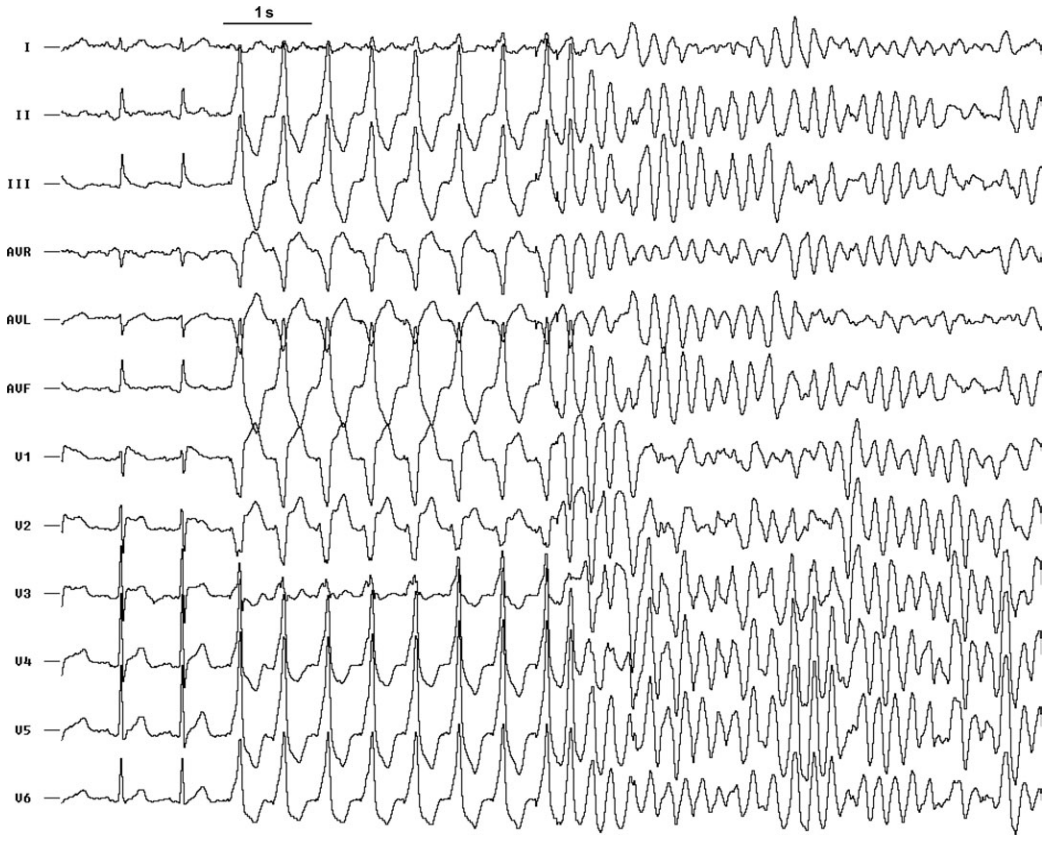

Figure 2 Induction of VF during programmed ventricular stimulation.

study showed an HV interval of 68 ms, and PA and AH intervals were normal. Programmed atrial stimulation did not induce any arrhythmia, whereas ventricular fibrillation (VF) was easily induced by single ventricular premature beat at a drive cycle of 500 ms from the right ventricular outflow tract: this required D.C. shock (*Figure 2*). The drug-challenge was performed by intravenous administration of ajmaline (1 mg/kg over 5 min) producing from the sixth minute, a new 'gigantic', 'coved-type', downsloping ST-segment elevation in leads II, III, and aVF, whereas the pre-existing ST-segment alterations in V1–V3 were normalized (*Figure 3*). During administration of the drug, the patient developed spontaneous polymorphic PVCs in pairs and triplets. The ST-segment elevation at the inferior leads completely resolved with the administration of isoprenaline (0.02 μg/mL/min) and the right precordial leads resumed the typical Brugada-pattern. An acute coronary syndrome was ruled out either by serial troponin T sampling and by coronary angiography during which no coronary spasm was induced by ergonovine provocation. The genetic assessment, in January 2004, to investigate the presence of *SCN5A* gene mutations proved negative.

As the patient had no signs of heart, pulmonary, neurological, or metabolic disease, we confirmed the diagnosis of Brugada syndrome with variant phenotype characterized by double localization of the typical ECG abnormalities and paradoxical effect of ajmaline administration. The clinical picture was characterized by a history of unexplained syncope and dizziness with palpitations, the easy induction of VF during EP study and the young age of the patient,

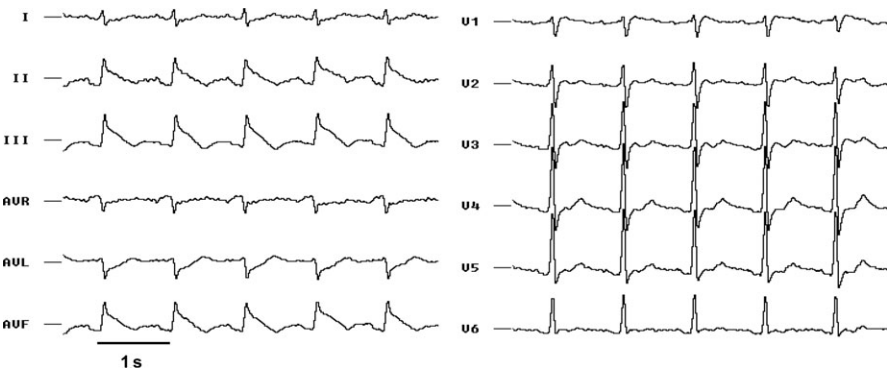

Figure 3 12-lead ECG, 6 min after administration of ajmaline showing prominent ST-segment elevation in the inferior leads, whereas the typical pre-existing Brugada abnormalities have completely resolved in V1–V3.

indicated the necessity to implant a cardioverter-defibrillator.

Discussion

Our case is the first description of a paradoxical effect of ajmaline on ECG abnormalities in a patient with Brugada syndrome featuring an alteration of typical ECG-phenotype from the right precordial leads to the inferior leads.

In the 90 s, association between idiopathic VF and ST-segment elevation with prominent J-wave in the inferior leads had been reported in southeast Asian patients.[7–10] More recently, anecdotal reports of patients with Brugada syndrome and anomalous localization of ECG-phenotype confined to the inferior leads have also been published.[11–14] Potet *et al*.[13] identified, in members of a French family, a novel G752R *SCN5A* mutation leading to a typical ST-segment elevation and prominent J-wave either in the inferior or in the right precordial leads. Moreover, the proband showed spontaneous typical Brugada ECG-phenotype restricted to the inferior leads. On pharmacological testing with flecainide, he displayed aggravation of ST-segment elevation in the inferior leads and new appearance of drug-induced ST-segment elevation in the right precordial leads. Our patient was in contrast to that of Potet *et al*.[13] as on drug-challenge with ajmaline, the pre-existing and typical ECG abnormalities in V1–V3 fully resolved but appeared in leads II, III, and aVF. More recently, Riera *et al*.[14] presented a case of spontaneous fatal VF in a young man with Brugada syndrome whose ECG at rest showed a persistent down-sloping ST-segment elevation in leads II, III, and aVF with specular horizontal ST-depression in V4 and V5 mimicking acute subendocardial ischaemia. Unfortunately, the patient had nocturnal sudden cardiac death and no pharmacological tests or genetic studies were available.[14]

In the concealed form of Brugada syndrome, a drug-challenge with class-I antiarrhythmics can unmask the ECG abnormalities by sodium channel blockade, enhancing the effect of the transient outward current (I_{to}) on the action potential.[5,6] As the transient outward current is better represented on the right ventricular than on the left ventricular epicardium, the transmural (epicardium–endocardium) voltage gradient is amplified in the right precordial leads where usually the typical ECG repolarization abnormalities are displayed.[15–19]

We speculate that localization of Brugada ECG-phenotype in the inferior leads is likely to be multifactorial. The following hypothetical explanations are possible: (1) a higher density of I_{to} as well as a lower density of I_{Na} in the inferior wall, rather than in the right ventricle; (2) an anomalous quantitative and qualitative distribution of ionic channels in the inferior wall because of an undetectable organic disorder (e.g. ischaemia or infection) leading to myocardial fibrosis; (3) greater parasympathetic innervation or sympathetic dysfunction of the inferior wall. All these conditions may be responsible for hypersensitivity to ajmaline which was localized to the inferior wall, determining the appearance of typical Brugada pattern in the inferior leads. In contrast, administration of isoprenaline, a β-agonist, normalized ECG abnormalities in the inferior leads probably via augmentation L-type calcium current (I_{Ca}) resulting in a restored local balance of inward and outward currents.

The atypical effect of drug-challenge on the right precordial leads in our patient remains unexplained. The contrasting effects of ajmaline and isoprenaline on the ECG changes which may be interpreted either as an unknown local paradoxical effect of ajmaline on sodium channels because of the genetic abnormality, or as reciprocal manifestation of the ST-segment elevation in the inferior wall annulling the effect on the anterior wall.

In our patient the double localization of the typical Brugada-pattern and the paradoxical effect of ajmaline on the ECG abnormalities confirmed the possibility of phenotype heterogeneity in the Brugada syndrome. However, in our patient, the suspicions of Brugada syndrome were based on spontaneous and typical ECG abnormalities in the right precordial leads, with changes in the inferior leads being drug-induced.

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