Brugada Syndrome Diagnosed After Sudden Cardiac Arrest

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In the early 1990s, Brugada and colleagues reported on 8 patients with recurrent syncopal attacks and remarkable electrocardiographic (ECG) findings that included right bundle branch block (RBBB), an elevated ST segment in the right-sided chest leads (V_1 and V_2), and a normal QT interval; they referred to this entity as *Brugada syndrome.*[1] The ECG manifestations of Brugada syndrome may be dynamic or concealed. If the patient is asymptomatic, ECG findings of Brugada syndrome may be unmasked or modulated by a number of drugs (eg, α-adrenergic agonists, β-adrenergic blockers) or clinical conditions (eg, febrile state, electrolyte abnormalities).[2–10] Diagnosis is important because patients with Brugada syndrome are predisposed to develop polymorphic ventricular tachycardia and sudden cardiac death. This article describes the case of a woman with Brugada syndrome who was diagnosed after an episode of sudden cardiac arrest.

CASE PRESENTATION

Initial Presentation

A 53-year-old woman from the Dominican Republic was brought to the emergency department (ED) after a successful resuscitation for a presumed ventricular fibrillation (VF)–induced cardiac arrest. She was in a restaurant having a meal when she suddenly lost consciousness and fell face forward into her food. Cardiopulmonary resuscitation was started in the field; emergency medical services personnel arrived shortly thereafter and delivered 3 shocks with an automatic external defibrillator for presumed coarse VF (**Figure 1**). The patient regained sinus rhythm with a heart rate of 126 bpm and a blood pressure of 126/90 mm Hg. She was intubated in the field.

Evaluation in the ED

Upon arrival in the ED, the patient was unresponsive to voice and painful stimuli, but vital signs were stable (blood pressure, 137/80 mm Hg; heart rate, 107 bpm; temperature, 96.9°F; and oxygen saturation, 99%). The physical examination was unrevealing except for the neurologic examination, which showed mid-sized pupils nonreactive to light and the absence of corneal reflexes. Posturing (flexion of the right forearm and extension of the other extremities) was also noted. Deep tendon reflexes were symmetric and Babinski reflexes were downgoing. The remainder of the physical examination was unremarkable.

Results of initial blood testing are shown in **Table 1.** The bicarbonate level was low, bilirubin was increased, and transaminitis was noted, all of which were considered consequences of cardiopulmonary resuscitation. An ECG was performed (**Figure 2**), and the cardiology service was consulted. The patient developed 2 more episodes of VF in the ED and was externally defibrillated, each time with return of sinus rhythm. An amiodarone drip was started in hopes of preventing further episodes of VF. Because the patient's serum potassium level was low (2.7 mEq/L), potassium was administered intravenously.

Questioning of the patient's sisters and husband revealed that the patient had been relatively healthy except for 2 episodes of syncope over the past 4 years. At that time, an extensive work-up was performed, including an ECG (**Figure 3**) and echocardiographic stress test, which was reported as normal. Both previous episodes occurred shortly after drinking alcoholic beverages and resolved within a few seconds without any known sequelae. There was no family history of heart disease or sudden cardiac death. Although the patient was not taking prescription medications, she had been taking over-the-counter herbal medicines, including the weight loss supplement Herbalite (calcium pyruvate, L-phenylalanine, citrus aurantium, *Garcinia cambogia*,

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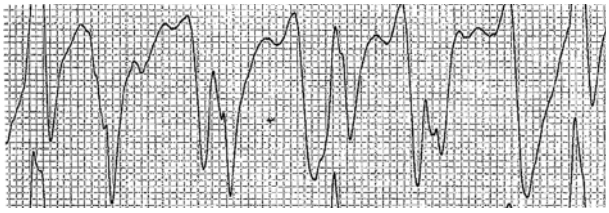


Figure 1. Initial electrocardiogram of the case patient obtained en route to the hospital demonstrating an uninterpretable rhythm through chest compressions.

olive leaf extract, green tea, gotu kola, eleuthero, stevia, manganese chelate, and chromium polynicotinate) as well as black cohosh for menopausal hot flashes. After the ECG was reviewed (Figure 2) and the history was obtained from the patient's sisters and husband, a presumptive diagnosis of Brugada syndrome was made and the amiodarone drip was stopped. The patient was transferred to the cardiac care unit (CCU) for further management.

Course in the CCU

Over the next 24 hours, the patient received aggressive management in the CCU with a detailed focus on her mental status and respiratory function. The patient's mental status quickly improved; in less than 12 hours she was awake and following simple requests, and her previous pathologic and neurologic findings returned to normal. On hospital day 2, she was extubated. Impaired recent retrograde memory was noted, which markedly improved over the subsequent 72 hours without any neurologic interventions. Daily ECGs during the patient's stay in the CCU (leads V_1–V_3) are shown in **Figure 4**. A signal-average ECG was negative (no evidence of late depolarization potentials), and magnetic resonance imaging of the heart to evaluate for arrhythmogenic right ventricular dysplasia (ARVD) was normal with no evidence of right ventricular infiltrative disease. At this time, the combination of typical ECG findings for Brugada syndrome, history of unexplained syncopal attacks, witnessed cardiac arrest, and negative results on signal-average ECG and magnetic resonance imaging established the diagnosis of Brugada syndrome.

Management

An automatic internal cardiac defibrillator (ICD) was implanted to prevent sudden cardiac death from ventricular arrhythmias and the patient was discharged home on hospital day 5. Because Brugada syndrome is linked to a multitude of genetic mutations, the patient's family was screened for a history of prodromal syndromes and sudden cardiac death, and ECGs were obtained from all family members in the immediate area. **Figure 5** shows the ECGs of some of the patient's family members (leads V_1–V_3). The ECG for the patient's daughter was significant for an incomplete RBBB, with less than 1-mm ST-segment elevation in V_1 and a negative T wave. Although the ECG was not normal, it does not fit into any of the described ECG patterns for Brugada syndrome. The ECGs for the patient's sisters showed no abnormalities. The ECG for the patient's mother showed a left bundle branch block, which was due to a previous myocardial infarction.

Table 1. Initial Results of Laboratory Tests for the Case Patient in the Emergency Department

Laboratory Test	Patient Value	Normal Range
Sodium (mEq/L)	140	135–145
Potassium (mEq/L)	2.7	3.5–5.0
Chloride (mEq/L)	108	98–107
Bicarbonate (mEq/L)	17	22–28
Blood urea nitrogen (mg/dL)	13	8–20
Serum creatinine (mg/dL)	0.8	0.6–1.2
Magnesium (mg/dL)	2.1	1.6–2.5
Calcium (mg/dL)	9.2	8.6–10.0
Albumin (g/dL)	3.7	3.4–4.7
Bilirubin (mg/dL)	2.5	0.1–1.2
Aspartate aminotransferase (U/L)	198	0–35
Alanine aminotransferase (U/L)	344	0–35
Alkaline phosphatase (U/L)	86	41–133
Creatine kinase (U/L)	163	32–267
Troponin I (mg/mL)	0.0	0.0–0.2
Ethyl alcohol (mg/dL)	26	Toxic > 100

BRUGADA SYNDROME

Epidemiology

In the 1980s, the Centers for Disease Control and Prevention reported a high incidence of sudden death in young immigrants from Southeast Asia.[11] Interestingly, natives of this region have long been aware of this problem of sudden unexpected death, known as *lai tai* (death during sleep) in Thailand, *bangungut* (scream followed by sudden death during sleep) in the Philippines, and *pokkuri* (unexpected sudden death at night) in Japan.[12–16] Recently, it has been recognized that many of these patients suffer from Brugada syndrome.[17]

Because the ECG pattern in Brugada syndrome can be dynamic, the syndrome's incidence and prevalence are difficult to estimate. However, it is thought that Brugada syndrome may cause 4 to 10 sudden

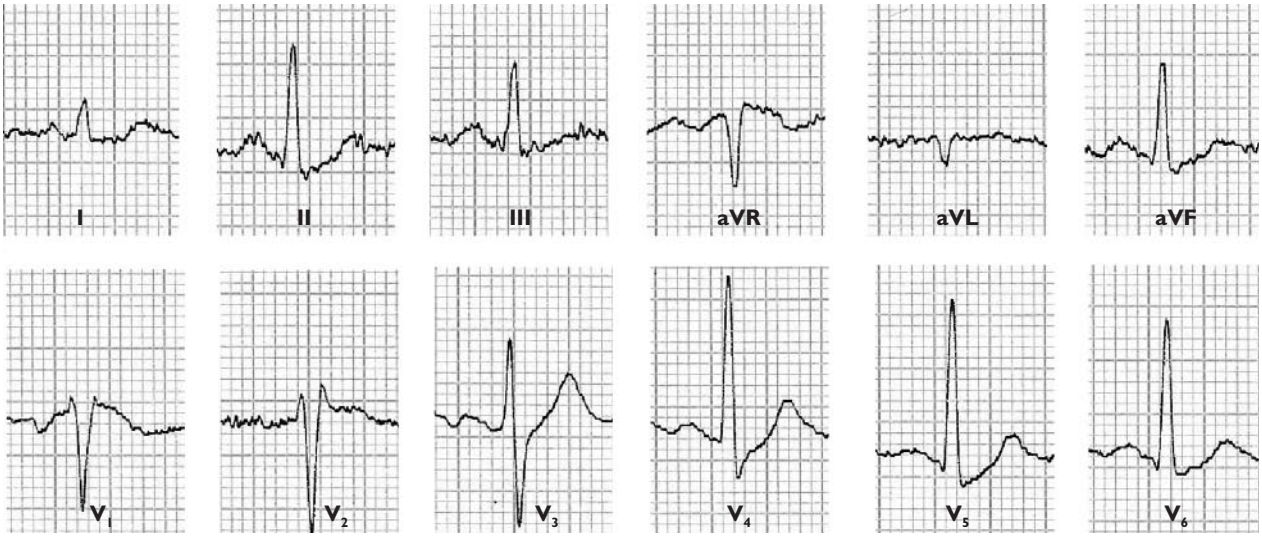


Figure 2. 12-Lead electrocardiogram of the case patient obtained on presentation to the emergency department demonstrating incomplete right bundle branch block pattern with an rSR' pattern and ST-segment elevation in leads V_1 and V_2.

deaths per 10,000 inhabitants in Southeast Asia annually, which would make it the second most common cause of natural death in men aged younger than 40 years.[2,17,18] In endemic countries, Brugada syndrome has been estimated to cause at least 4% of all sudden deaths and at least 20% of all sudden cardiac deaths in patients with structurally normal hearts.[2,3] In Laos, Brugada syndrome causes an estimated 1 sudden death per 1000 inhabitants per year, and in Thailand, unexpected sudden death is the most common cause of natural death in young people.[2,3] Brugada syndrome is an autosomal dominant disorder, which explains the higher prevalence in some areas.

In epidemiologic surveys, the "Brugada sign" on ECGs has a reported prevalence of 0.05% to 0.16%.[19,20] In a large urban teaching hospital in the United States, the characteristic ECG pattern of Brugada syndrome was found in 0.4% of patients.[21] In the Hispanic population, the prevalence of this pattern is unknown.

Etiology

Brugada syndrome has been linked to a genetic mutation located on the *SCN5A* gene, which codes for the α subunit of the cardiomyocyte sodium ion channels. This mutation leads to either complete loss of channel function or an accelerated recovery from activation. This can generate heterogeneity of repolarization and increase the chance of intramyocardial re-entry circuits, which may induce ventricular tachyarrhythmias.[17,22,23] SCN5A mutations account for 18% to 30% of cases of Brugada syndrome.[24]

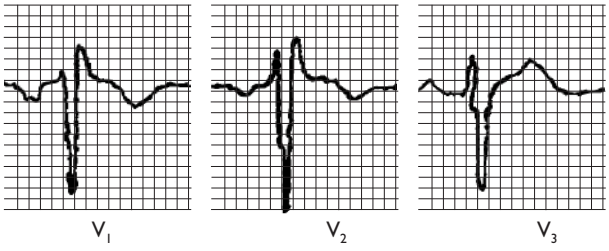


Figure 3. Leads V_1, V_2, and V_3 of a 12-lead electrocardiogram (ECG) demonstrating incomplete right bundle branch block. The ECG was performed as part of the work-up for syncope 3 years prior to this admission.

Clinical Manifestations and ECG Findings

Brugada syndrome typically presents during adulthood, with a mean age of sudden death at approximately 40 years. It can also present with supraventricular arrhythmias, such as atrial fibrillation, which is present in 10% to 20% of cases. Potential clinical manifestations of Brugada syndrome include dizziness, palpitations, syncope, and sudden cardiac death.[2] Brugada syndrome is associated with an ECG pattern consisting of a pseudo-RBBB and persistent ST-segment elevation in leads V_1 to V_3. Guidelines from the second consensus conference on Brugada syndrome define 3 ECG patterns (**Table 2** and **Figure 6**).[2,25,26] Type 1 (cove-type) Brugada pattern is the classic ECG pattern of the syndrome; it includes an elevated ST segment that descends with an upward convexity into an inverted T wave. In type 2 and type 3, the ST segment has a saddleback configuration in which the elevated ST segment descends toward the baseline

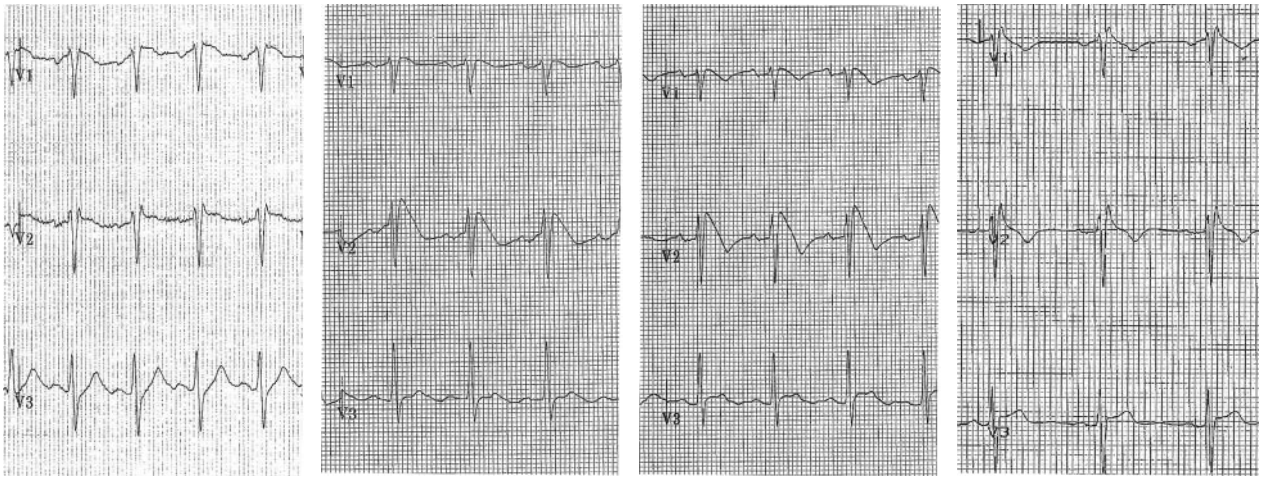
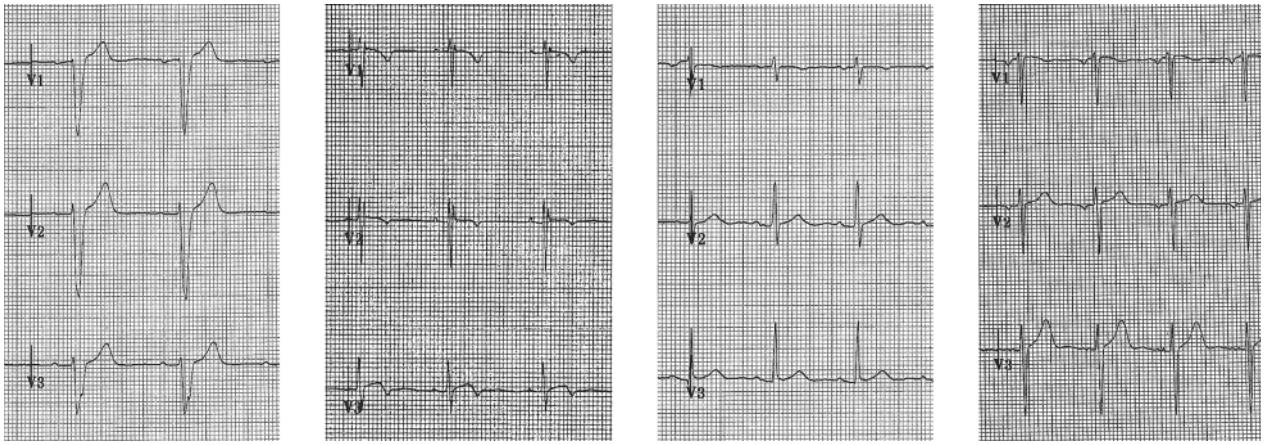


Figure 4. Serial electrocardiograms performed over the first 48 hours after the case patient's admission demonstrating some dynamic changes on the precordial leads V_1 through V_3. These electrocardiographic changes are typical of Brugada syndrome, with coved ST-segment elevation ending in an inverted T wave (more notable in leads V_1 and V_2).



Mother | Daughter | First sister | Second sister

Figure 5. Selected electrocardiograms (ECGs; leads V_1–V_3) from some of the case patient's family members. The ECG of the mother demonstrates a left bundle branch block. The ECG of the daughter shows an incomplete right bundle branch block with less than 1-mm ST-segment elevation and a negative T wave, but these findings are not characteristic of Brugada syndrome. The ECGs for both sisters show no abnormalities.

and then rises again into an upright or biphasic T wave. In addition, a slight prolongation of the QT interval may be present along with ST-segment elevation in Brugada syndrome.[27]

The ECG manifestations of Brugada syndrome are often dynamic or concealed and may be exposed or modulated by sodium channel blockers (class Ia, Ic, and III antiarrhythmic medications), fever, vagotonic agents, α-adrenergic agonists, β-adrenergic blockers, tricyclic antidepressants, a combination of glucose and insulin, hypokalemia and hyperkalemia, hypercalcemia, and alcohol or cocaine toxicity. Adrenergic stimulation has also been shown to decrease ST-segment elevation, whereas vagal stimulation increases ST-segment elevation.[28–30] Shifting of the right precordial leads to the second and third intercostal space may reveal a type 1 Brugada ECG pattern. It is believed that the Brugada sign is a reflection of conduction delay localized in the right ventricular anterior wall and the right ventricular outflow tract.[2,31] Because of the dynamic ECG presentation of Brugada syndrome, it is important to consider this condition in the differential diagnosis of patients with syncope or sudden cardiac arrest. Conditions that can mimic Brugada syndrome are shown in **Table 3**.

In the case patient, Brugada syndrome was diagnosed

Table 2. ECG Characteristics of Brugada Syndrome

Type	Characteristic
Type 1	A coved ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave. Definitively diagnostic when observed in > 1 right precordial lead (V_1–V_3) in the presence or absence of a sodium channel–blocking agent and in conjunction with 1 of the following: documented VF, polymorphic ventricular VT, a family history of sudden cardiac death at age < 45 yr, coved-type ECGs in family members, inducibility of VT with PES, syncope, or nocturnal agonal respiration
Type 2	Saddleback appearance with a high takeoff ST-segment elevation and then either a positive or biphasic T wave
Type 3	Either a saddleback or coved appearance with an ST-segment elevation of < 1 mm

NOTE: Diagnosis of Brugada syndrome is also confirmed if a type 2 or type 3 ECG pattern is present at baseline and then converts to diagnostic type 1 pattern after sodium channel blocker administration. One or more of the clinical criteria should also be present.

Data from Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association [published erratum appears in Circulation 2005;112:e74]. Circulation 2005;111:659–70.

ECG = electrocardiogram; PES = programmed electrical stimulation; VF = ventricular fibrillation;VT = ventricular tachycardia.

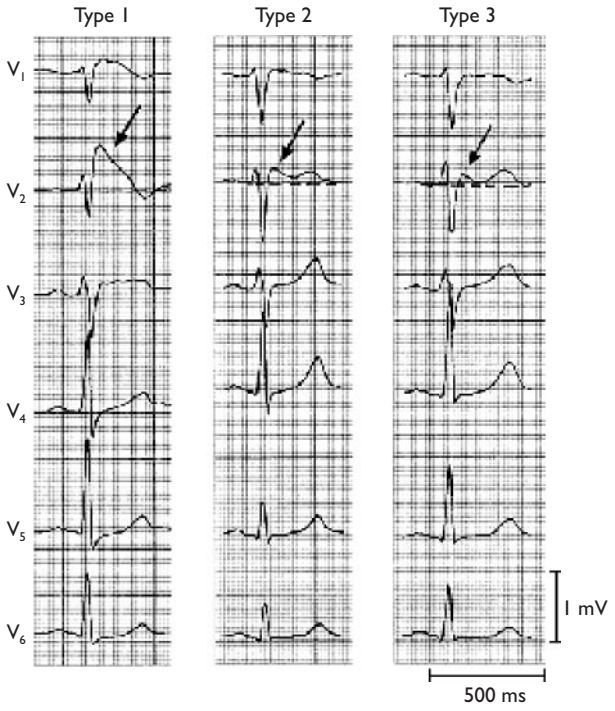


Figure 6. Patterns of ST-segment elevation in Brugada syndrome. Arrows denote the J wave. (Adapted from Wilde AA, Antzelevitch C, Borgreffe M, et al. Proposed diagnostic criteria for Brugada syndrome. Eur Heart J 2002;23:1649. Copyright 2002 with permission from Elsevier.)

based on the ECG presentation consistent with type 1 Brugada pattern and her history of 2 syncopal episodes prior to the VF arrest. However, even when symptoms and ECG findings suggestive of Brugada syndrome are present, definitive diagnosis usually occurs in the electrophysiology laboratory, where malignant arrhythmias may be induced pharmacologically or electrically. Whether this patient's VF episode was triggered by her over-the-counter weight loss regimen, sensitivity to alcohol ingestion, or an autonomic imbalance could not be determined.

The ECG pattern of Brugada syndrome can be an early subclinical manifestation of ARVD. In an autopsy study of 96 young victims of sudden cardiac death with available baseline ECGs, 14% had right precordial ST-segment elevation with or without RBBB; at autopsy, all but 1 had pathologic changes consistent with ARVD.[32]

Management

Placement of an ICD is the only proven effective measure available for treatment of Brugada syndrome. There is no consensus on the best course of management for asymptomatic family members who manifest ECG patterns consistent with this syndrome. Recently, Glatter et al[33] reviewed the approach to evaluation and treatment of such patients and concluded that at this time there are insufficient data to support treatment of asymptomatic patients with Brugada ECG patterns. The guidelines proposed by the second consensus conference on Brugada syndrome recommended the use of electrophysiology studies (EPS) in asymptomatic

Table 3. Differential Diagnosis of Brugada Syndrome

Atypical right bundle branch block
Left ventricular hypertrophy
Early repolarization
Acute pericarditis
Acute myocardial ischemia (septal or right ventricular myocardial infarction)
Prinzmetal's angina
Duchenne muscular dystrophy
Hyperkalemia
Hypercalcemia
Arrhythmogenic right ventricular dysplasia
Pectus excavatum
Hypothermia
Thiamine deficiency

patients with a family history of sudden death who also have type 1 Brugada ECG patterns.[2] However, this approach is not accepted by all study groups. For instance, data have consistently failed to show that EPS identify higher-risk patients.[34] Another recently published study by Eckardt et al[35] also questioned the predictive value of EPS in these patients. The reasons for the different results for the predictive ability of EPS are not clear. One explanation might be that there is no universally accepted EPS protocol for testing people with Brugada ECG pattern.[33–35]

Currently, the need for ICD placement and treatment for asymptomatic patients with Brugada ECG patterns is also controversial. Longer follow-up studies are needed to clarify this issue.

CONCLUSION

Although Brugada syndrome is relatively uncommon, its association with sudden cardiac death mandates its prompt recognition and treatment. Clinicians must be aware of characteristic ECG findings that may point to dangerous conditions, such as short and long QT syndromes, ARVD, and, of course, Brugada syndrome. This case illustrates the importance of carefully evaluating patients with episodes of syncope as well as the value of identifying the etiology of sudden cardiac arrest and the subsequent need for treatment. Because Brugada syndrome is hereditary, family members of patients diagnosed with this condition should be approprately screened. **HP**

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