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Review

Epidemiology of Brugada syndrome in Japan and rest of the world

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ABSTRACT

Brugada syndrome is an inherited disease that causes sudden death because of ventricular fibrillation. Its prevalence is approximately 0.15% in adults and 0.005% in children in Asia, and less than 0.02% in the West. The reason for the higher prevalence in Asia is likely ethnic-specific polymorphisms modulating the activity of the primary disease-causing mutation. In Japan, the incidence of Brugada-pattern electrocardiogram (ECG) is 14.2 per 100,000 person-years. Data from multicenter registries indicate that its frequency in men with Brugada syndrome is higher in Japanese patients (94–96%) than in Caucasian patients (72–80%). Healthy individuals with Brugada-type ECG have a favorable prognosis with an annual death rate of less than 0.5%.

Contents

1. Introduction

Brugada syndrome (BS) is a clinical entity that causes sudden death because of ventricular fibrillation (VF) in patients with apparently structurally normal hearts, and it is characterized by coved ST-segment elevation in the right precordial leads (V1–V3) [1,2]. A similar clinical condition, which brings sudden death mainly at night in young and middle-aged men, has been known in Asian countries by different names such as “pokkuri” in Japan, “lai-tai” in Thailand, and “bangungut” in the Philippines. Several cases of pokkuri or idiopathic VF that showed coved ST elevation just after resuscitation were reported in Japan [3,4] in 1990 (Fig. 1) before Brugada et al. first described this condition in 1992. In 1990, we also reported that some patients demonstrate a peculiar ST elevation in the leads V1–V3 and develop a syncopal attack at midnight or early morning in a series of four cases with idiopathic VF [4].

With respect to the ST elevation in the precordial lead, Antzelevitch et al. demonstrated that this can be an expression of early repolarization or J-wave caused by transient outward current (I_{to})-mediated transmural differences in the early phases of the action potential. BS is an inherited disease with a heterogeneous genetic basis [5]. More than 11 genes have been linked to this disease in the last 15 years, although mutations in *SCN5A* are the most commonly found mutations in 15–30% of Brugada patients.

2. Prevalence of Brugada syndrome in Japan

BS is responsible for 4% of all sudden deaths and for up to 20% of sudden deaths in patients without structural heart disease [2,6]. The estimated prevalence of BS ranges from 4 to 122 per 10,000 inhabitants in Japan. However, many of these reports were published before 2002 when the consensus report for BS was proposed [7]; thus, the 12-lead electrocardiogram (ECG) definition in many reports included not only the coved ST elevation but also the saddleback ST elevation with a J-wave of amplitude ≥ 1 mm

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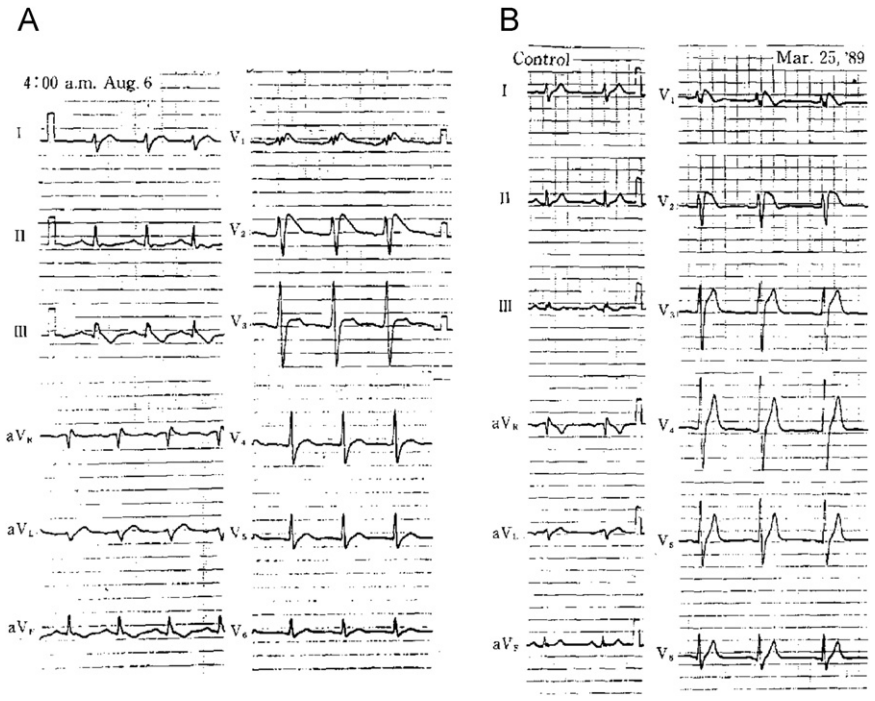

Fig. 1. 12-Lead ECGs of a case who recovered from "pokkuri". A 41-year-old man was admitted to the local hospital for syncope accompanied by agonizing respiration at night. A 12-lead ECG on admission at 4:00 AM on 6 August 1988 showed a prominent coved ST elevation in leads V1 and V2 without T-wave inversion (Fig. 1A). These T-waves became inverted 7 months after admission (25 March 1989), although the coved ST elevation in leads V1 and V2 continued to be observed (Fig. 1B). Modified, with permission, from Motoki and Tsujimura [3].

(0.1 mV). Furthermore, right bundle branch block (RBBB) was considered to be an essential ECG feature for BS at that time. Miyasaka et al. reported that the coved ST elevation ≥ 1 mm with RBBB was found in 0.12% of 13,929 subjects, with a prevalence of 0.38% in men and 0.03% in women, who were screened during annual health examinations in Moriguchi-city, Osaka [8]. They also indicated that Brugada-pattern ECG was recognized in 0.7% of all subjects but was higher in men (2.14%) when saddleback ST elevation ≥ 1 mm was also included in the Brugada-pattern. In the same study cohort in Moriguchi, Tsuji et al. later reported that 0.26% of subjects demonstrated type 1 Brugada-pattern ECG with or without RBBB [9]. Atarashi et al. evaluated 10,000 ECGs obtained during annual check-ups of working adults in the Tokyo area and found that 16 men (0.16%) showed coved-type ST elevation ≥ 1 mm with RBBB in the right precordial leads [10]. In addition, Matsuo et al. reported that the prevalence of Brugada-pattern ECG with coved or saddleback ST elevation ≥ 1 mm was 0.146% in a survey of ECG records of 4788 atomic-bomb survivors who underwent biennial health examination for 40 years in Nagasaki [11]. Furuhashi et al. also reported that the prevalence of Brugada-pattern ECG was 0.14% in 8612 healthy subjects [12]. A report with an inclusion criterion for Brugada-type ECG of ST elevation >2 mm with or without RBBB was published by Sakabe et al. [13]. They evaluated ECGs of 3339 healthy adult subjects who underwent medical examinations annually from 1992 to 2001 and reported that an average 0.28% of subjects showed coved-type ST elevation in the right precordial lead. They also indicated that the majority (97%) of subjects who showed coved-type or saddleback-type ST elevation (1.22%) were men.

Oe et al. studied the prevalence of BS in juveniles [14]. They reported that only one (0.005%) of 21,944 first-year elementary school children (6–7 years old) showed a type 1 ECG, and three showed type 2 or type 3 ECGs. Yamakawa et al. investigated the prevalence of Brugada-type ECG (types 1–3) in 20,387 school children between the first grade and tenth grade (from primary school to high school) [15]. They found that only one (0.07%) male student (15 years old) showed a type 1 ECG and one female student (15 years old) showed a type 2 ECG among 1328 high school students. In addition, none of the younger children showed type 1 ECGs, and nine school children had coved or saddleback ST elevation with J-wave amplitude between 1 mm and 2 mm. They also demonstrated that the prevalence of the Brugada-pattern ECG increased with age (first graders, 0.01%; fourth graders, 0.05%; seventh graders, 0.08%; and tenth graders, 0.23%).

Although typical Brugada-type ECG does not always appear and the ECG changes can fluctuate over time, these results indicate that the Japanese prevalence of BS or type 1 ECG, which is recorded on the standard 12-lead ECG without any provocation methods, can be estimated to be less than 0.005% in children and between 0.12% and 0.28% in adults.

3. Prevalence of Brugada syndrome in the rest of the world

The prevalence of BS is lower in Western countries than in Japan, even when the classification of Brugada-type ECG is required to have a J-wave amplitude ≥ 2 mm and type 1 ECG is required to have an inverted T-wave, because most studies have been conducted after 2002 when the consensus report was published. Data from the Copenhagen City Heart Study, Denmark, in which a total of 42,560 ECGs were registered from 18,974 participants, showed no type 1 Brugada-pattern and 14 type 2 or 3 patterns [16]. In that study, Pecini et al. reported that the prevalence of BS was 0% and that of Brugada-type ECG was 0.07%, although the representative ECG of the type 2 Brugada-pattern clearly showed coved ST elevation with T-wave inversion in lead V2 [16]. Junttila et al. investigated the prevalence of BS in 2479 young subjects and 542 middle-aged subjects in the Finnish population and found no type 1 ECG and 15 (0.61%) type 2 or 3 ECGs [17]. Sinner et al. reported that not a single individual showed a Brugada-type ECG in the investigation of 12-lead resting ECGs of 4149 German subjects [18]. Letsas et al. reported

the prevalence of Brugada-type ECG among 11,488 ECGs recorded in a Greek tertiary hospital; 0.02% of subjects demonstrated type 1 ECGs and 0.2% demonstrated type 2 or 3 ECGs [19]. In a report from Italy and the United Kingdom, 0.016% of 12,012 healthy subjects showed type 1 ECGs and 0.26% showed Brugada-type ECGs [20]. Likewise, Brugada-type ECG has infrequently been identified in the United States (0.012%) [21] and in Canada (0.07%) [22]. The prevalence of Brugada-pattern ECG with J-wave amplitude ≥ 1 mm was reported by Hermida et al. from France [23]. They reported that the typical coved pattern was identified in 0.1% and the saddleback pattern was observed in 6% of 1000 subjects.

In contrast, the prevalence of BS or Brugada-type ECG in Asian countries is relatively high. Type 1 ECG has been identified in 0.17% of 3907 asymptomatic Filipinos [24] and in 0.13% of 20,652 Taiwanese patients who visited the hospital for non-cardiovascular reasons [25]. Brugada-type ECG has been observed in 0.9% of 10,867 young, healthy Korean men [26]. At a heart rhythm clinic in Singapore, 12 of 392 male patients (3.1%) showed type 1 ECGs and 28 (7.1%) showed Brugada-type ECGs [27]. In Pakistan, the Brugada-type ECG pattern frequency was reported to be 0.8% [28]. The prevalence of BS in the southern Turkish population seems to show an intermediate value compared to that in Asian and Western countries. Bozkurt et al. reported that one of 1238 subjects (0.08%) demonstrated a type 1 ECG and five (0.74%) showed type 2 or 3 ECGs [29]. Overall, the prevalence of BS in adults is estimated to be around 0.15% in Asian countries, including Japan, between 0.1% and 0.02% in Middle Eastern countries, and less than 0.02% in Western countries.

As for the reason why the prevalence is high in Asian people, it has been reported that common ethnic-related genetic polymorphisms might modulate the activity of the primary disease-causing mutation or influence susceptibility to arrhythmia. Bezzina et al. identified a haplotype variant consisting of six individual DNA polymorphisms, designated haplotype B, in near-complete linkage disequilibrium within the proximal promoter region of the *SCN5A* gene in Asians only and not in Caucasians or African-Americans [30]. They concluded that haplotype B does not give rise to BS, but it likely contributes to a higher incidence of BS in the Asian population.

4. Incidence of Brugada syndrome in Japan

Matsuo et al. reported that the incidence of Brugada-pattern ECG, including coved and saddleback ST elevation ≥ 1 mm was 14.2 persons per 100,000 person-years in a 40-year survey of 4788 atomic bomb survivors < 50 years of age in Nagasaki [11]. This rate was nine times higher among men than women (31.4 vs. 3.5 persons, respectively, per 100,000 person-years), and the average age at presentation was 45 ± 10 years, although the peak incidence was observed in patients in their thirties.

5. Gender difference in Brugada syndrome

Despite the equal genetic transmission of the mutation between the sexes, the clinical phenotype is much more prevalent in men than in women. In Japan, community-based population studies have revealed that Brugada-pattern ECGs (coved or saddleback ST elevation ≥ 1 mm) predominate in men ($> 90\%$). Miyasaka et al. reported that the prevalence in men was 0.38% in contrast to 0.03% in women [8]. In another cohort study in which 41% of the subjects were men, the percentage of men with Brugada-pattern ECG was 84% [11]. On the other hand, men with Brugada-pattern ECG comprised 97% of all Brugada subjects in a cohort study that included 79% men [13] and 100% in a study that included 89% men [10]. Tsuji et al. reported that the frequency of men with type 1 ECG was 84% in a survey in which 26% of all ECGs were obtained from men [9]. The data from multicenter BS registries indicate that the frequency of men with type 1 ECG was 94–96% [31,32]. Therefore, the sex-adjusted rate of type 1 ECG in adult men probably reaches 90–96% in Japan. The frequency of boys in the first grade with Brugada-pattern ECG was reported to be 50% [14] (two in 11,282 boys vs. two in 10,662 girls), but it became 90% after the fourth grade [15].

Regarding this gender difference in BS, Di Diego et al. suggested a cellular basis for the male predominance in BS using arterially perfused canine right ventricular (RV) wedge preparation [33]. They reported that the I_{to}-mediated phase 1 action potential notch in the RV epicardium, which was larger in male dogs than in female dogs, was responsible for the male predominance of the Brugada phenotype. Shimizu et al. suggested that the level of the male hormone, testosterone, which is reported to increase the outward potassium currents, was significantly higher and body mass index (BMI) was significantly lower in men with Brugada than in the controls [34]. In addition, Tsuji et al. reported that the BMI of subjects with the Brugada-pattern ECG was significantly lower than that of subjects without BS in a study with a large number of subjects [9]. The fact that the testosterone levels in males peak during the teen and early adult years and the incidence of Brugada-pattern ECG peaks in the thirties [11], even though the genders show a similar prevalence in childhood [14], may suggest that gender differences are linked to the testosterone level depending on age.

Letsas et al. reported that the prevalence of Brugada-type ECG was 0.34% in men and 0.04% in women in the Greek population [19]. Despite the similar BS gender differences between the Greeks and the Japanese, many multicenter studies performed in Western countries indicated that the frequency of men with BS (72–80%) [35–39] was much lower than that of the Japanese population (94–96%) [31,32]. The reason for this national difference in gender-related frequency in BS is not completely understood. Racial difference or higher BMI in Caucasian men might have an influence on the severity of Brugada phenotype manifestation. Another reason may be the difference of BS cohorts between Western multicenter studies and Japanese BS registries. The former included a significant number of family members in whom type 1 ECG was induced by drug provocation tests, while the latter mainly consisted of probands who had spontaneous type 1 ECG. The fact that patients with a milder phenotypic expression of BS make up a considerable proportion of subjects in studies from Western countries, may result in the higher rate of inclusion of women in Western registries.

6. Prognosis of healthy individuals showing Brugada-pattern ECG

The prognosis of healthy subjects with Brugada-pattern ECG or Brugada-type ECG is favorable. Miyasaka et al. reported that one of 98 subjects with Brugada-pattern ECG with a J-point elevation ≥ 1 mm and 139 of 13,831 controls died during 2.6 ± 0.3 years of follow-up [8]. Matsuo et al. reported that seven of 32 subjects with Brugada-pattern ECG developed unexpected death in contrast to 20 of 4736 subjects with normal ECG during 40 years of follow-up [11]. Cox survival analysis revealed that mortality was significantly higher in subjects with Brugada-pattern ECG than in control subjects. Sakabe et al. reported that one of 69 subjects with Brugada-type ECG with a J-wave amplitude ≥ 2 mm had an episode of ventricular fibrillation during 4 years of follow-up [13]. Tsuji et al. reported that one of 98 subjects with Brugada-type

ECG and 142 of 13,806 controls developed cardiovascular death during 7.8 ± 1.6 years of follow-up, although no one with type 1 ECG died [9]. With regard to juveniles, Oe et al. [14] reported that none of the four subjects with Brugada-type ECG had an episode of sudden death or syncope during 6.8 ± 1.0 years of follow-up.

The outcome of healthy subjects with Brugada-type ECG is much better in Western countries. No cardiovascular death or life-threatening ventricular arrhythmia was observed in 25 individuals during 29.7 ± 10.7 months of follow-up in a Greek population [19], in 15 subjects during 19 ± 2 years of follow-up in a Finnish population [17], and in seven subjects for more than 30 years of follow-up in a Danish population [16]. However, one of 31 subjects died suddenly during 10.1 ± 5.5 years of follow-up in an English and an Italian population [20]. Sixty-one subjects showing Brugada-pattern ECG in a French population did not die from cardiovascular disease during 49 ± 30 months of follow-up [23]. To summarize, the annual death rate of healthy adults with Brugada-pattern or Brugada-type ECG is estimated to be less than 0.5%.

7. Conclusions

The prevalence of type 1 ECG in the healthy Asian population is considered to be around 0.15% in adults and 0.005% in children. However, it is considered to be less than 0.02% in the Western population. The prognosis of these subjects is expected to be good, and the annual death rate is expected to be less than 0.5%.

Conflict of interest

The author has no conflicts of interest to disclose.

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