CASE REPORT

Type 1 Brugada pattern ECG due to supra-therapeutic phenytoin level

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SUMMARY

Brugada syndrome is an inherited arrhythmogenic disease, characterised by a coved-type ST segment elevation in right precordial leads and an increased risk of sudden cardiac death due to ventricular arrhythmia. To unmask or exacerbate a Brugada ECG pattern, class IA or IC antiarrhythmic agents are used, and clinicians can predict sudden cardiac death in a high-risk patient. However, phenytoin, one of the class IB agents, may induce a Brugada pattern ECG at a supra-therapeutic level and this association has rarely been reported. We describe a case of a patient with a phenytoin level about twice as high as the therapeutic level, which led to the emergence of a type 1 Brugada pattern ECG. Awareness should be made between this important association of supra-therapeutic phenytoin level and type 1 Brugada pattern ECG because symptomatic Brugada syndrome can lead to sudden cardiac death.

BACKGROUND

Brugada syndrome (BS) is an inherited arrhythmogenic ion channel disease that can lead to ventricular arrhythmias, syncope and sudden death. It was first described as a distinct clinical entity in 1992.¹ There are three different ECG patterns, however, each should appear in more than one right precordial lead (V1 to V3) in patients with BS. Type 1 is characterised by a prominent coved ST segment elevation displaying J-point amplitude or ST segment elevation ≥ 2 mm, followed by a negative T wave. Type 2 also has a ≥ 2 mm J-point elevation, ≥ 1 mm ST segment elevation and a saddleback appearance, followed by a positive or biphasic T wave. Type 3 ECG revealed either a saddleback or coved appearance, but with an ST segment elevation < 1 mm. However, clinicians should keep in mind that type 1 is the only ECG diagnostic pattern of BS while types 2 and 3 should only be considered suggestive of the disease.^{2,3}

Drug challenge for diagnosis of BS is indicated in high-risk patients, for familial screening and in suspicious patients with normal resting ECG. Flecainide, ajmaline, procainamide, disopyramide and propafenone are class IA and IC antiarrhythmic drugs (AAD) that have been used to unmask BS.⁴ However, phenytoin, a class IB AAD anticonvulsant agent, may induce a type 1 Brugada pattern ECG at supra-therapeutic level; this association has rarely been reported.

CASE PRESENTATION

A 54-year-old male wheelchair user with a medical history of cerebral palsy (CP), scoliosis and seizure

disorder, presented to the emergency department (ED), with symptoms of right thigh pain for 4 days. He was accompanied by his mother; at the time of the event, he was trying to move from bed to chair, and fell and hit his buttocks on the floor. However, he denied head injury or loss of consciousness, and X-rays of the right knee were negative. His hip pain was increasing and X-ray of the right hip revealed a right hip fracture. He was then admitted to the hospital. He denied chest pain, dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, palpitations, dizziness, headache, syncope, presyncope, seizure, history of heart attack, arrhythmia, blurred vision, and urinary and bowel problems. The episode of falling at home before he came to ED was thought to be a mechanical fall. His last seizure episode had been 9 months prior. Home medications included acetaminophen 650 mg orally every 6 hours as needed, and phenytoin 300 mg orally daily. There was no family history of sudden death, heart attack, congenital cardiac diseases or arrhythmia. The patient denied smoking cigarettes, drinking alcohol and recreational drug use.

Initial vital signs included temperature 98.1°F, pulse rate 98 bpm, respiratory rate 16 breaths per minutes, blood pressure 116/78 mm Hg and oxygen saturation 98% on room air.

Physical examination revealed a normal head and neck, and normal respiratory function with no crepitation and no rhonchi. Cardiovascular examination showed normal apex beat without thrill or heave. The point of maximal impulse was not displaced. Auscultation revealed normal regular first and second heart sounds with neither murmur, rub nor gallop. Abdominal examination was within normal limit. Neurological examination showed an awake and alert man, oriented to time, place and person; contracture of the right arm and painful right hip with external rotation and the rest of the physical examination could not be performed because the patient refused these.

INVESTIGATIONS

Laboratory tests showed a normal comprehensive metabolic panel including normal electrolyte levels with potassium 3.9 mmol/L, magnesium 2 mg/dL and calcium 9.1 mg/dL. Other tests showed albumin 2.9 g/dL, troponin < 0.01 ng/mL, B-type natriuretic peptide 20.5 pg/mL, serum creatinine 0.6 mg/dL and estimated glomerular filtration rate 149.23 mL/min. Complete blood count, coagulation profile and chest X-ray were within normal limits. X-ray of the right hip was consistent with fracture. Serum total phenytoin level was 38.4 μ g/mL.

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Figure 1 Coved-type ST segment elevations with negative T wave in V1-V2 consistent with type 1 Brugada pattern.

(normal: 10–19.9 µg/mL) and corrected phenytoin level was 40.8 µg/mL. Echocardiogram was within normal limits. ECG demonstrated a new right bundle branch block pattern with coved ST segment elevations and inverted T wave in leads V1-V2, consistent with type 1 Brugada pattern ECG (figure 1).

TREATMENT

The phenytoin was held and the patient was put on cardiac monitoring. ECG and phenytoin level were monitored daily from the first day of admission. However, the phenytoin level was still supra-therapeutic and serial ECGs still showed a type 1 Brugada pattern. On day 5 of hospital stay, the ECG returned to baseline and the Brugada pattern was no longer observed on ECG (figure 2).

The repeat serum phenytoin level on that day was 14.4 µg/mL. Serial cardiac enzymes were normal and there was no arrhythmia event noted on cardiac monitoring. An orthopaedic operation was performed after the phenytoin level was within normal limits and after the Brugada pattern ECG had resolved. Later, the patient was enrolled in a physical therapy rehabilitation programme. The phenytoin was restarted at 300 mg orally

daily and the serum phenytoin level was within therapeutic range for 3 to 4 days at the same dose. The patient was then discharged at the same dose of phenytoin 300 mg orally daily. His high-serum phenytoin level on admission was likely due to an overdose of phenytoin, since he had a poor memory, and a lack of understanding of how to correctly take medications and of their exact dosages. The patient had been experiencing a worsening memory problem for more than 2 years. He had been followed by a neurologist for his history of CP and his memory problem had been assessed using the Mini-Mental State Examination (MMSE). MMSE score was 20. The patient had been taking phenytoin for more than 10 years. Requesting for a social worker was discussed and a visiting nurse service was arranged on his discharge to supervise the patient on how to correctly take his medications. Drug interaction was unlikely as far as we know.

OUTCOME AND FOLLOW-UP

The patient remained asymptomatic throughout the hospital course and was discharged. Both the patient and his family members were advised to follow-up with a cardiologist or an electrophysiologist, however, they refused.

Figure 2 Disappearance of ST elevation and T wave inversions in V1, V2.

DISCUSSION

Phenytoin, an antiepileptic drug, has class IB antiarrhythmic drug (AAD) properties, and is a potential treatment for patients with refractory ventricular arrhythmia when other agents are contraindicated or unavailable. It effects on the sodium channels in cardiac myocyte and Purkinje fibre cell membranes.⁵ It decreases the maximum rate of depolarisation of the cardiac action potential and increases the effective refractory period. Therefore, it is useful in inhibiting ventricular ectopy, especially in an ischaemic or damaged myocardium.⁶ However, the emergence of newer and less toxic agents has led to the replacement of phenytoin as a first-line treatment.

Our case demonstrated that phenytoin at a supra-therapeutic level induced a type 1 Brugada ECG pattern, which is a coved-type ST segment elevation and T wave inversions in V1 and V2. The mechanism is likely because of phenytoin's sodium channel blocking activity, which facilitates the loss of dome of right ventricular epicardial action potential by changing the balance of current at the end of phase 1.⁷ Miyazaki *et al* reported on two patients who received a class IB AAD (mexiletine 125 mg or lidocaine 100 mg) at normal doses and failed to produce a Brugada pattern ECG. However, a possible reason behind this was that class IB AADs are less potent than class IA or IC are, and may require supra-therapeutic levels to achieve sodium channel blockage.⁸ Al Aloul *et al*⁹ also reported emergence of a type 1 Brugada pattern ECG with serum phenytoin level of 22 µg/mL and normalisation of ECG after the phenytoin level was found to be within therapeutic range.

In addition, patients with a spontaneously appearing Brugada ECG have a high risk for sudden arrhythmic death due to ventricular tachycardia/fibrillation,³ and individuals found by chance to have a spontaneously abnormal ECG during screening should undergo programmed ventricular stimulation for appropriate risk stratification. If the patients are inducible, Brugada P *et al*¹⁰ recommended the implantation of an implantable cardioverter defibrillator. If they are non-inducible, conservative management and follow-up are advised. However, Eckardt *et al*¹¹ concluded in a study with 212 patients with a type 1 Brugada ECG pattern that a very low incidence of severe arrhythmic events was found after more than 2 years follow-up and programmed electrical stimulation revealed very little accuracy in predicting outcome. Decision to follow-up with a cardiologist or a rhythm specialist depends on the patient's age, family history, prior episodes of syncope due to cardiac disorders and the patient's preferences.

While our patient's fall was assumed to be a mechanical fall due to pre-existing CP-induced muscle weakness, syncope due to arrhythmia should be differentiated from syncope after seizure episodes. In some patients with Brugada syndrome, syncope or sudden cardiac death (SCD) is the only presenting symptom. Rapid polymorphic ventricular tachycardias are found as the underlying cause. About 80% of patients with documented ventricular fibrillation have a history of syncope.¹² Some patients with seizure disorder have an increased risk for sudden unexplained death.¹³ A study has shown that sudden death in patients with Brugada syndrome most commonly occurs during sleep, especially during the early morning hours.¹⁴ Also, Parisi *et al*¹⁵ found a genetic association between Brugada syndrome and epilepsy, in which a known mutation in the SCN5A gene (p.W1095X, c.3284G>A) was identified.

Furthermore, patients on phenytoin should have serum levels checked in the perioperative period. Birnbaum *et al*¹⁶ reported that measurement of a single total phenytoin concentration

should not be used to guide the management since there is significant variability in total phenytoin concentration in an observational study in elderly nursing home residents taking phenytoin. Lalitha *et al* also mentioned considerable variability of phenytoin levels in patients in an intensive care unit (ICU), with a difference of more than 100% between the highest and lowest phenytoin level in individual cases. Therefore, periodic serum phenytoin level should be checked even in absence of seizures or signs of phenytoin toxicity among patients in ICU who are on the same dose of phenytoin.¹⁷

To conclude, phenytoin at a supra-therapeutic level may unmask a type 1 Brugada pattern ECG. Awareness of type 1 Brugada pattern ECGs should be made by neurologists and primary care physicians because symptomatic Brugada syndrome can lead to SCD. Therefore, serum phenytoin level and ECG should be performed in all patients with seizure who are taking phenytoin.

Learning points

- ▶ Brugada syndrome (BS) is an inherited arrhythmogenic ion channel disease that can lead to ventricular arrhythmias, syncope and sudden death.
- ▶ A type 1 Brugada pattern ECG is characterised by a prominent coved ST segment elevation displaying J-point amplitude or ST segment elevation ≥ 2 mm, followed by a negative T wave in more than one right precordial lead (V1-V3). This type of ECG is the only ECG diagnostic pattern of BS.
- ▶ Drug challenge for diagnosis of BS is indicated in high-risk patients, for familial screening or in suspicious patients with normal resting ECG. Class IA and IC antiarrhythmic drugs (AAD) have been used to unmask BS.⁴ However, phenytoin, a class IB AAD anticonvulsant agent, may induce a type 1 Brugada pattern ECG at supra-therapeutic level; the association has rarely been reported.
- ▶ There is considerable variability of total serum phenytoin concentration while patients are on the same dose. A single total phenytoin concentration is not sufficient enough to guide treatment. Periodic serum phenytoin levels should be checked even in absence of seizures or signs of phenytoin toxicity among patients in ICU.
- ▶ Awareness of type 1 Brugada pattern ECGs should be made by neurologists and primary care physicians because symptomatic Brugada syndrome can lead to sudden cardiac death. Therefore, serum phenytoin level and ECG should be performed in all patients with seizure who are taking phenytoin.

Competing interests None declared.

Patient consent Obtained.

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