CASE REPORT

Sinus pauses and high-grade atrioventricular block in Albright's hereditary osteodystrophy with pseudopseudohypoparathyroidism

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SUMMARY

Albright's hereditary osteodystrophy (AHO) is a rare inherited syndrome involving the molecular defects in the gene encoding the α subunit of the stimulatory G protein (Gs α). AHO has several variants, mainly pseudohypoparathyroidism (PHP) and pseudopseudohypoparathyroidism (PPHP). We present a family that share the same inactivating GNAS1 mutation, the daughter being affected by PPHP and her late father with PHP. The daughter, in her late teens, presented with a long history of presyncopal and syncopal attacks. Her father died suddenly in his mid-40 s. As expected, her laboratory tests to date have shown normal biochemistry and hormonal levels. Subsequently, an implantable loop recorder was inserted. This demonstrated extreme sinus pauses of >11 s and also high-grade atrioventricular block. A dual-chamber pacemaker was therefore inserted.

BACKGROUND

This case is the first to illustrate an association of sinus pauses and atrioventricular (AV) block with pseudopseudohypoparathyroidism (PPHP).

CASE PRESENTATION

A girl in her late teens was referred following several years' history of presyncopal and syncopal attacks. She is also known to have PPHP. Over the years these symptoms have been put down to possible epilepsy, vasovagal attacks and some to panic attacks. At the age of 6 she was treated with anti-epileptic medication, however, owing to her drowsiness while taking the medication her parents decided to stop it a few days later. She had never received any other medications.

Her father had pseudohypoparathyroidism (PHP) which was caused by the GNAS1 gene fault. He, however, died unexpectedly in his mid-40s. Postmortem could find no obvious pathology that could have caused his death. A presumed sudden cardiac death was postulated. Her mother, although not submitted to formal IQ assessment, appeared to have learning difficulties and her elder sister died in her infancy of a brain tumour. No other relatives were accessible for examination.

Genetic testing was completed when she was 14-years-old. It showed she had inherited her father's causative GNAS1 gene mutation. As a child she had developmental delay, delayed puberty and menstruation, mild asthma and learning difficulties.

Figure 1 Photographs of hands.

Despite this, she attended college undertaking a course in animal care.

On examination she is a petite, thin girl and of short stature. Although it is not particularly striking, she demonstrated relatively short fifth digits, with slightly shorter thumbs (figures 1 and 2). She also has scars on her knees from having her subcutaneous calcification removed. Her blood pressure was 95/60. Her heart sounds were normal with no murmurs.

INVESTIGATIONS

She has never had any biochemical or hormonal irregularities throughout her life.

The EEG and MRI of her brain have been reported as essentially normal, ruling out epilepsy.

A 24-hour-ECG was carried out and this has shown sinus rhythm with first degree and occasionally second degree type 1 AV block. She later on

Figure 2 Photographs of hands.

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Figure 3 Implantable loop recorder showing sinus pauses > 11 seconds.

had a cardiac event recorder which made a number of recordings during symptomatic periods. However, the recordings showed only sinus rhythm on each occasion. She went on to have an echocardiogram which showed normal cardiac dimensions with good left ventricular function and very mild anterior mitral leaflet prolapse.

As her syncopal episodes continued, an implantable loop recorder (ILR) was then inserted. Initial interrogations did not show any significant abnormalities. A year later, the recordings demonstrated extreme sinus pauses of >11 s and high-grade AV block (figure 3).

DIFFERENTIAL DIAGNOSIS

The identification of the causes of syncope is often not straightforward. The key concern is to recognise the potentially lethal causes. Careful history and examination are therefore essential in approaching syncopal individuals.¹

Cardiac syncope is associated with adverse outcomes, and potentially death. The causes include structural cardiac abnormalities and cardiac electrical disorders. Cardiac manifestations of Albright's hereditary osteodystrophy (AHO) are not well reported. They are usually related to biochemical abnormalities that can occur in AHO, commonly hypocalcaemia. These include hypocalcaemic dilated cardiomyopathy with systolic left ventricular dysfunction,² atrial septal defect,³ coarctation of the aorta,⁴ hypocalcaemic-induced long QT⁵ and hypocalcaemic-induced ventricular arrhythmia.⁶

Seizures, usually grand mal, have been described in AHO. There are multiple reasons accounting for seizures in AHO. These include worsening hypocalcaemia and calcium deposition

in the brain.^{7 8} However, it has also been noted that seizures in AHO can be independent of hypocalcaemia.⁹

Another common cause of syncope is vasovagal syncope. Vasovagal syncope occurs when the body over-reacts to triggers. Usually occurring in a standing position, precipitating factors include unpleasant sights, fear, extreme emotion and pain. Autonomic activation prior to losing consciousness, for example flushing and sweating, suggests a vasovagal origin. The pathophysiology of vasovagal syncope is not completely understood; however, familial cases of vasovagal syncope have been described although not in AHO. Interestingly, one study involving 137 patients with syncope has found an association between the predisposition to vasovagal syncope and mutation within the codon encoding GNAS1 (FokI+ allele).¹⁰ This study, however, did not involve any patients with AHO.

TREATMENT

A dual chamber pacemaker was implanted.

OUTCOME AND FOLLOW-UP

She had no further syncope and her symptoms have improved following the pacemaker implant.

DISCUSSION

AHO is a rare hereditary syndrome exhibiting characteristic phenotypic abnormalities, typically distinctive skeletal and developmental defects. AHO is associated with either the presence (PHP) or absence (PPHP) of multihormone resistance. AHO is transmitted as an autosomal dominant trait.^{11–13}

AHO is because of the defects identified in the GNAS-1 gene. GNAS-1 is located on chromosome 20q13. It encodes the

stimulatory G protein α subunit ($G\alpha$), a key component of many signal transduction pathways. Mutations will result in a protein with defective function as well as a 50% reduction in $G\alpha$ levels in erythrocytes.^{9 14}

PHP, a complex endocrine disorder, was first described by Albright *et al* in 1942. Albright *et al* described a group of patients with clinical and chemical findings of hypoparathyroidism, but resistant to parathyroid hormone (PTH) rather than deficient. This disorder is manifested by hypocalcaemia, hyperphosphataemia but raised serum immunoactive PTH levels. In addition, their clinical syndrome was characterised by brachydactyly mostly affecting the fourth and fifth rays, short stature, round face, obesity, subcutaneous ossifications, learning difficulties, developmental delay and neurobehavioural problems.^{11 15} Today, PHP has been further classified into types Ia, Ib, Ic and type II¹⁶ based on phenotypic and biochemical findings.

PPHP was coined in 1952 by Albright and his associates. It is named for its similarity to PHP (type Ia), but without hormone resistance.¹⁷ They have PHP phenotype, a normal renal response to PTH but reduced levels of $G\alpha$. This is owing to the parental imprinting of the *GNAS* gene. Maternal inheritance/imprinting results in PHP, in which the disease is fully expressed. Paternal inheritance/imprinting results in PPHP, in which the disease is partially expressed and does not display hormonal resistance.^{14 16}

Musculoskeletal abnormalities are the most frequent malformations reported with AHO. Cardiovascular abnormalities associated with AHO however, are rare and generally associated with hypocalcaemia. In addition, to our knowledge, the association of cardiac arrhythmias in AHO with normal biochemical findings has never been described.

In this report, syncope and bradyarrhythmias represent the major features of this patient's clinical presentation. The European Society of Cardiology and the American Heart Association/American College of Cardiology have published guidelines in approaching patients with syncope. The identification of high-risk syncopal individuals requires a careful history, examination and a 12-lead ECG. These will guide subsequent evaluation for the need of further non-invasive or invasive testing modalities to confirm the diagnosis.¹ An echocardiogram is a helpful screening test in confirming or refuting the presence of structural heart disease as well as risk stratifying individuals based on the left ventricular ejection fraction.^{1 18 19}

In selected patients, further specialised tests can be pursued to aid suspected diagnoses. Exercise stress test is a valuable tool to evaluate exertional syncope in which potential causes include obstructive or ischaemic sources. During an exercise stress test, a drop in blood pressure or if blood pressure fails to rise, raises the suspicion of hypertrophic obstructive cardiomyopathy or left main stem coronary artery disease in patients less than 40 years of age.^{1 18 19}

ILRs are recommended for patients with recurrent syncope of uncertain origin, in whom extensive work up failed to lead to a diagnosis or specific treatment. These devices are inserted subcutaneously and may be implanted for up to 36 months. Commonly observed rhythms with these devices include transient bradyarrhythmias.^{1 18 19} Our patient presented with recurrent, although infrequent, syncope in which the diagnosis was between epileptic seizure and cardiac syncope. She did not reveal any abnormalities during her extensive neurological and cardiological work-up. An ILR was implanted, 17 months later she was found to have bradyarrhythmias.

Invasive electrophysiological study (EPS) is a minimally invasive study which identifies the cause of syncope by inducing a

tachyarrhythmia. It is most useful for identifying ventricular tachyarrhythmias and the risk of death in patient with ischaemic heart disease with syncope.^{1 18 19} EPS provides limited value in diagnosing bradycardia-mediated syncope.

Bradyarrhythmias are comprised of a number of rhythm disorders including sinus node dysfunction and AV node dysfunction. Sinus node dysfunction includes sinus pauses and sinoatrial bradycardia. Transient but profound sinus pauses longer than 3 s during waking hours and severe sinus bradycardia lower than 40 bpm may result in syncope owing to a neurocardiogenic reflex. In this circumstance, pacemaker therapy is usually appropriate. First- and second-degree heart block do not commonly present with syncope. However, the presence on ECG monitoring of third-degree AV block is a Class I indication for permanent pacing.¹⁹ Our patient was treated with a pacemaker and she has been free from attacks since then.

The findings in this case also support previous reports that suggest arrhythmic syncope is more likely than epileptic seizures in syncopal individuals with normal EEG and neuroimaging, despite normal cardiological findings.²⁰

Learning points

- ▶ This case is the first of its kind to report the relationship of pseudopseudohypoparathyroidism (PPHP) with normal calcium metabolism and cardiac bradyarrhythmias.
- ▶ The malignant risk of these arrhythmias mandates prompt recognition and therapy.
- ▶ This case is reported to raise attention, and to encourage further studies that correlate between PPHP, syncope and susceptibility to cardiac bradyarrhythmias.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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