New disease

Accelerated coronary atherosclerosis and H syndrome

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Summary

A 12-year-old boy with insulin dependent diabetes mellitus, presented with acute myocardial infarction. Intracoronary thrombolysis with urokinase restored TIMI III flow in the culprit vessel. After stabilisation with medical therapy, unusual clinical findings in the form of cutaneous hyperpigmentation and hypertrichosis, affecting the lower extremities, were appreciated. These and other phenotypic features were consistent with H syndrome, a recently described autosomal recessive genodermatosis, and confirmed by mutation analysis. Despite being on optimal medical therapy for coronary artery disease, the patient presented 3 months thereafter, with unstable angina which was successfully managed with percutaneous coronary intervention. An unusual occurrence of coronary artery disease with accelerated atherosclerosis in a child with H syndrome is presented herein. Identification of further patients with this novel disorder will clarify the possible association, suggested here, with increased risk for coronary or other vascular events.

BACKGROUND

H syndrome, an autosomal recessive multisystem genodermatosis, was initially recognised as a disease entity in 2008. To date, more than 50 patients with phenotypic features consistent with this disorder have been described in the medical literature. Despite the wide range of systemic manifestations characterising H syndrome, thrombotic events have not been previously reported.

We present the unusual occurrence of atherosclerotic coronary artery disease with rapid progression, in a 12-year-old boy with H syndrome. As this is the first H syndrome patient reported to develop a vascular event, a possible association is discussed.

CASE PRESENTATION

A 12-year-old male, the youngest of three siblings, born to non-consanguineous parents of Indian origin, was referred for evaluation of typical anginal chest pain of 18 h duration. His medical history included insulin dependent diabetes mellitus (IDDM), diagnosed at the age of 1.5 years and sensorineural hearing loss of 1 year duration. At the time of admission, the patient was haemodynamically stable (Killip class I). All the peripheral pulses were well felt and no bruits were heard. His ECG showed ST elevation in the inferior and lateral leads (figure 1A). Echocardiography revealed hypokinesia of the baso-lateral, basal and mid inferior segments of the left ventricle, with preserved systolic function and no other significant structural lesions. Troponin T was elevated (1.03 ng/ml; normal <0.1 ng/ml). A presumptive diagnosis of acute myocardial infarction was made. He was administered oxygen, morphine, sublingual nitrate, 325 mg chewable aspirin, 150 mg clopidogrel and 25 mg metoprolol tartrate in the emergency department. In view of persistent chest pain and a window period of more than 12 h, a coronary angiogram (CAG) was planned to confirm the clinical diagnosis as well as to undertake a

possible percutaneous coronary intervention (PCI). CAG showed thrombus in the proximal left circumflex (LCX) artery with TIMI II flow (figures 2A,B). There was no evidence of spontaneous dissection. The left main coronary artery (LMCA), left anterior descending artery (LAD) and right coronary artery (RCA) profiled in multiple views were normal. Intracoronary thrombolysis was planned and 50000 units of urokinase were administered. A repeat angiogram after bolus administration of urokinase revealed complete dissolution of the thrombus without any residual lesion (figures 2C,D). Prompt relief of angina with ST segment resolution was observed (figure 1B). Subsequently, the patient received 12 u/kg/h of heparin infusion for 48 h with frequent monitoring of activated partial thromboplastin time and platelet count. There was no recurrence of angina and his further in-hospital course was uneventful.

Following the acute events, further attention was given to several unique clinical findings in this patient. Indurated pigmented hypertrichotic patches were noted over the lower extremities and lower back (figure 3A). These were reported to appear initially at age 9 years on the medial aspects of both feet and thereafter had a progressive course, spreading to the dorsum of his feet, the flexor and extensor aspects of the thighs, buttocks and lower back. The knees were spared (figure 3B). The anthropometric measures of height, weight and body mass index (120 cm, 25 kg and 17.3, respectively) revealed short stature and underweight. Hepatomegaly, with a liver span of 13 cm, micropenis and hallux valgus were also noted on physical examination. Ophthalmic examination revealed arcus senilis and normal fundus.

INVESTIGATIONS

Laboratory studies revealed microcytic hypochromic anaemia (haemoglobin-6.1 g/dl) with elevated erythrocyte sedimentation rate (70 mm/h) and C-reactive protein of 5.5 mg/

Figure 1 ECG during index hospitalisation. (A) ECG on admission showing ST segment elevation in the inferior and lateral leads. (B) ST segment resolution after intracoronary administration of urokinase.

dl. Random blood sugar was 181 mg/dl with HbA1c of 7%. Renal and liver function tests were normal. The patient's lipid profile was as follows: Total cholesterol of 113 mg/dl, high-density lipoprotein (HDL) cholesterol of 29 mg/dl, low-density lipoprotein cholesterol of 65 mg/dl, serum triglycerides of 96 mg/dl, very low-density lipoprotein cholesterol of 19 mg/dl and lipoprotein (a) (Lp(a)) of 105 mg/dl (normal <30 mg/dl). Follicle stimulating hormone and luteinizing hormone levels were low (0.96 mIU/ml and <0.07 mIU/ml; reference range of 1.4–18.1 mIU/ml and 0.1–6.0 mIU/ml, respectively). Antinuclear antibodies and direct Coomb's test were negative. Prothrombin time, baseline activated partial thromboplastin time and thrombin time were within normal limits. Lupus anticoagulant and anti-cardiolipin antibodies were negative. Antithrombin activity was within the biological reference interval. Protein C, free protein S, fibrinogen and homocysteine levels were normal. Audiometry confirmed sensorineural hearing loss. Contrast echocardiography with micro-bubbles did not reveal right to left intracardiac shunting.

The constellation of the clinical and laboratory findings led to the diagnosis of H syndrome. This was confirmed by mutation analysis of SLC29A3 which revealed a homozygous missense mutation in exon 4 (R133C). Both parents were found to be heterozygous for the mutation and the mutation was absent in the elder, unaffected sibling. The patient's eldest sister who died of pneumonia at the age of 13, was also known to suffer from IDDM, diagnosed at age two and a half. She was reported to have a similar pattern of cutaneous hyperpigmentation starting

at age 9 years. Taken together, most likely she was also affected with the H syndrome. The patient was discharged with aspirin, clopidogrel, ramipril, metoprolol tartrate and atorvastatin.

FOLLOW-UP

The patient was asymptomatic for 3 months following the described coronary event. However, the patient subsequently presented with recurrent episodes of angina at rest (Braunwald class III B). The ECG revealed dynamic ST depressions in V2–V4 with no evidence of reinfarction. Cardiac biomarkers were negative and left ventricular systolic function was normal, with no new regional wall motion abnormality. Appropriate measures for acute coronary syndrome were promptly initiated. A repeat CAG revealed distal LMCA bifurcation disease (50% stenosis) with a 90% narrowing of the ostio-proximal LAD and ostial LCX (figure 2E). The lesions persisted despite administration of 200 mcg of intracoronary nitroglycerine. Revascularisation options; coronary artery bypass surgery (CABG) versus PCI were discussed with the child's parents. The parents opted for PCI. Since the LCX was non-dominant and infarct related, a 3.5×15 mm endeavor stent (Medtronic Inc, Minneapolis, Minnesota, United States) was placed across the distal LMCA upto the proximal LAD. It was inflated upto 14 atmospheres. Significant residual narrowing was seen in the stent. Postdilatation was performed using a non-compliant balloon. The waist gave way at 20 atmospheres indicating that the lesion was extremely fibrotic. Pinching of the LCX was observed (figure 2F). However, no ECG

Figure 2 (A–D) Coronary angiogram (CAG) during index hospitalisation. (E, F) CAG during second admission for unstable angina. (A, B) CAG in right anterior oblique (RAO) caudal and left anterior oblique (LAO) caudal views depicting thrombus in the proximal left circumflex (LCX). The left main coronary artery (LMCA) and left anterior descending artery (LAD) are normal. (C, D) CAG demonstrating dissolution of thrombus without residual lesion after intracoronary administration of urokinase. (E) Repeat CAG after 3 months in RAO caudal showing distal LMCA bifurcation disease (50% stenosis) with a 90% narrowing of the ostio-proximal LAD and ostial LCX. (F) Result after deployment of drug eluting stent (DES) from distal LMCA to proximal LAD.

changes or enzyme elevations (troponin T, CPK-MB) were noticed after the procedure. In addition to dual antiplatelet therapy (aspirin, clopidogrel) and statin, extended release niacin (250 mg daily) was initiated in view of the low HDL and elevated Lp(a).

DISCUSSION

Myocardial ischemia and infarction are rare in the paediatric population. The aetiology may be either congenital, as a result of various congenital cardiac malformations (coronary arterial anomalies, transposition of the great vessels following an arterial switch procedure, aortic valvular

and supraventricular stenosis, pulmonary atresia) or acquired (autoimmune vasculitis, Kawasaki disease, trauma, or endocarditis).¹ Familial homozygous hypercholesterolemia, other conditions associated with dyslipidemia^{2 3} and prothrombotic disorders, especially when associated with coronary anomalies⁴ are also risk factors for premature coronary arterial disease in children and young adults. Although IDDM is associated with an increased risk of cardiovascular complications and early signs of atherosclerosis are often seen in children and adolescents with diabetes, these are clinically silent at this age and paediatric macrovascular complications are rare.⁵ Our patient presented with

Figure 3 Phenotypic characteristics. (A) Hyperpigmented, hypertrichotic patches over the lower extremities. (B) Dermatological lesions sparing the knee.

myocardial infarction at age 12 years. The characteristic cutaneous hyperpigmentation and induration, involving the lower half of his body, as well as additional clinical findings (IDDM, short stature, hepatomegaly, hallux valgus and sensorineural hearing loss) led to the diagnosis of H syndrome, which was confirmed by mutation analysis. H syndrome is a newly described autosomal recessive disorder characterised by cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, short stature (low height), hyperglycaemia/diabetes mellitus, hallux valgus and fixed flexion contractures of the toe and finger joints.^{6 7}

H syndrome was shown to be caused by mutation in SLC29A3 which encodes for hENT3, an intracellular nucleoside transporter.⁷ hENT3 is believed to function in facilitating transport of nucleosides and nucleoside analogues in both mitochondria and lysosomes. Mutations disrupting its function are assumed to alter nucleoside pools in these organelles and potentially interfere with various mitochondrial and lysosomal homeostatic functions.⁸ Since its original description,⁶ more than 50 patients were reported worldwide and our patient is only the second case reported from India.^{9–18} Interestingly, both Indian patients are homozygous for the same mutation, indicating a possible founder effect.¹³ This assumption is supported by the fact that both patients share the same haplotype. Nevertheless, despite having the same mutation, the previously reported patient did not have diabetes mellitus or acute coronary syndrome.¹³ This further demonstrates the variable clinical phenotype associated with the H syndrome. Of interest is the association of IDDM and deafness in our patient. This is the third report of this association^{13 16} indicating again that H syndrome and pigmented hypertrichotic dermatosis with insulin dependent diabetes, a so called allelic disorder to the H syndrome,¹⁷ actually represent the same disease entity. Various cardiac abnormalities have been described in patients with H syndrome; atrial septal defect,^{6 19}

ventricular septal defect,⁶ mitral valve prolapse,⁶ pulmonic stenosis,⁷ pericardial effusion or pericarditis,^{7 9 14 16} cardiomegaly or left ventricular dilation,^{6 9 20} cardiac septal thickening,⁷ thickening of posterior pericardium and right atrial wall,²¹ patent ductus arteriosus,^{7 19} left superior vena cava to coronary sinus,⁷ bicommissural aortic valve with mild aortic incompetence²¹ and pulmonary hypertension on echocardiography.^{6 7} The multiple cardiac anomalies associated with this disorder indicate a possible role for hENT3 in normal cardiovascular morphogenesis.

This is the first report of acute coronary syndrome in H syndrome. The pathogenesis of coronary artery disease in the present case is interesting. The localised involvement of the coronary artery at a bifurcation point may indicate an underlying plaque rupture with superimposed thrombus formation, secondary to premature atherosclerosis. The link between H syndrome and ischemic heart disease is not definitive. Long standing, especially poorly controlled diabetes is a well known risk factor for the development of macrovascular complications in adults. However, as mentioned previously, macrovascular complications of IDDM are rare in children, even more so in the prepubertal age group.^{5 22} The exact role of elevated Lp(a) as a cardiovascular risk factor is still debated.²³ The coronary event reported in our patient is therefore unlikely to be attributed only to the presence of IDDM and elevated Lp(a). Structural coronary abnormality which could have contributed to the event has not been identified by angiography or echocardiography. Importantly, the coronary lesions had progressed rapidly despite optimal therapy and in the second episode were highly fibrotic. These all suggest that additional, yet unknown risk factors may have contributed here, possibly related to the H syndrome. However, since this is the first H syndrome patient reported to have a vascular complication, it is still premature to determine whether this disorder carries an increased risk for cardiovascular events with accelerated progression.

The treatment of acute coronary syndrome in children is challenging since there are no definitive guidelines. Hence, decisions are to be adapted mainly from adult protocols. In view of varied aetiologies, diagnostic coronary angiography is mandatory in all cases. Therapeutic options include thrombolysis, anticoagulation, angioplasty with or without stenting and CABG.^{24 25} At the time of the first presentation, we preferred intracoronary thrombolysis over PCI or thrombus aspiration because of the anatomical location of the thrombus. Hence intracoronary urokinase was administered with clinical, electrocardiographic as well as angiographic resolution. In the subsequent admission, the relative merits of CABG and PCI were discussed with the parents.

Long-term outcomes with either modality in the paediatric age group are uncertain. A drug eluting stent was chosen in view of the anatomical location and the background history of IDDM. At present, there is no data to recommend long-term anticoagulation.

To conclude, H syndrome is a rare autosomal recessive genodermatosis with systemic manifestations. Clinicians should be aware of the diverse manifestations of this newly described condition. An unusual occurrence of coronary artery disease with accelerated atherosclerosis in a patient with H syndrome is presented herein. Identification of further patients suffering from this disorder will clarify the possible association, suggested here, with increased risk for coronary or other vascular events.

Learning points

- Unique pattern of pigmented hypertrichotic dermatosis with diverse systemic manifestations characterise the recently described H syndrome. It is an autosomal recessive genodermatosis caused by mutation in the nucleoside transporter hENT3.
- Multiple cardiac anomalies have been associated with H syndrome and may indicate a possible role for hENT3 in normal cardiovascular morphogenesis. However, vascular events have not been previously described in this disorder.
- We presented here the first case of accelerated coronary atherosclerosis in a paediatric patient with H syndrome. It is still premature to determine whether the H syndrome carries an increased risk for thrombotic events, however, increased recognition of this condition will shed light on this possible association.

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Competing interests None.

Patient consent Obtained.

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