Bronchiectasis in a Marfanoid: Diagnosis Beyond Marfans

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[Indian J Chest Dis Allied Sci 2014;56:105-107]

Introduction

Homocystinuria is an autosomal recessive inherited disorder usually diagnosed in childhood. It is an unusual cause of bronchiectasis in adults. We report a case presenting with bilateral cystic bronchiectasis and Marfanoid features. Associated deep vein thrombosis (DVT), mental retardation and history of childhood cataract surgeries aroused suspicion of homocystinuria. The diagnosis was confirmed by a positive urine examination for homocystinuria and elevated serum homocysteine levels.

Clinical Summary

A 35-year-old man, presented with cough with copious expectoration with postural variation and exertional dyspnoea since childhood. He had a past history of childhood surgery for cataract in both eyes and a previous surgery for a right-sided inguinal hernia. He had no addictions. There was a history of poor scholastic performance. He also gave a history of sibling death and recurrent abortions in mother. The family-tree is illustrated in figure 1. On clinical examination, the patient had Marfanoid features, i.e. tall, thin stature (dolichostenomelia), arm span more than height, arachnodactyly, positive wrist (Walker’s sign) and thumb sign (Steinberg sign). In addition, he had a left-sided femoral hernia and bilateral varicose veins with bilateral lower limb ulceration. Respiratory system examination on auscultation revealed bilateral coarse crackles.

Investigations

The haemogram, liver function test and renal function tests were normal. Chest radiograph (Figure 2) showed cystic lesions in the right lung, which were confirmed to be due to bilateral cystic bronchiectasis on high resolution computed tomography (HRCT) of thorax (axial and saggital sections; Figure 3A and B). Spirometry was suggestive of an obstructive abnormality. Two-dimensional echocardiography (2D ECHO) showed aortic root dilatation. Dual energy x-ray absorption (DEXA) scan documented osteopaenia. Lower limb venous Doppler showed a DVT in the right saphenous vein. Intelligent quotient (IQ) study revealed a moderate mental retardation. As the Ghent criteria for the diagnosis of Marfans syndrome were not fulfilled, the patient was considered to have Marfanoid features. Homocystinuria was suspected in view of DVT, mental retardation, history of childhood cataract surgeries in the presence of Marfanoid features. Serum homocysteine levels were obtained and found to be elevated at 57.64 µg/mL (normal range- 0.73-2.19). Urine examination detected homocysteine. Serum vitamin B12 level was normal.

Figure 1. Family-tree showing normal, carriers and affected members.

Figure 2. Chest radiograph (postero-anterior view) showing cystic bronchiectasis in the right lung.

[Received: June 20, 2013; accepted after revision: November 11, 2013]

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Thus, a diagnosis of classical form of homocystinuria was confirmed due to cystathionine beta synthase (CBS) enzyme deficiency. The patient was treated with pyridoxine and folic acid supplementation and diet modifications for homocystinuria; anticoagulants for deep vein thrombosis and bronchodilators, postural drainage and rehabilitation measures for bronchiectasis and associated chronic obstructive airway disease.

Diagnosis: Bronchiectasis due to homocystinuria

Discussion

Homocystinuria is an autosomal recessive inherited disorder of methionine metabolism. Neonatal screening is carried out for homocystinuria in developed countries. Deficiencies of CBS enzyme or methylene tetrahydrofolate reductase (MTHFR) enzyme cause homocystinuria. Mutations in CBS, MTHFR, MTR (5-methyl tetrahydrofolate-homocysteine methyltransferase), MTRR (methionine synthase reductase), and MMADHC (methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria) genes are cited. The classical form of homocystinuria is caused by the deficiency of CBS enzyme.

Clinical manifestations of homocystinuria are variable and depend on the age at presentation. Usually if missed at newborn screening, these patients present in early childhood to an ophthalmologist. Ectopia lentis inferiorly with high myopia is the classical finding. Later these patients present at various timelines with central nervous system, skeletal and vascular system abnormalities. Homocystinuria has several features in common with Marfans syndrome including dislocation of the lens; a tall, thin-build with long limbs; arachnodactyly; and a pectus deformity of the chest. Marfanoid features, subluxated lenses, bronchiectasis, hernia and varicose veins represent manifestations of fibrillin deficiency. The thrombotic episodes are due to increased procoagulants, thromboxane A2 and cofactors. Central nervous system involvement is secondary to thrombotic events and homocysteine toxicity. Osteopaenia occurs because homocysteine interferes with the correct formation of intra-chain and inter-chain bonds in the early post-translational modification of collagen.

Respiratory system involvement in homocystinuria has been reported in the form of primary spontaneous pneumothorax, unilateral hyperlucent lung, pulmonary thromboembolism, and restrictive abnormalities due to scoliosis. Bronchiectasis secondary to homocystinuria is a rare and unusual finding reported at few countable instances. In a case series of 24 homocystinuria patients studied in Saudi Arabia only one had bronchiectasis. Center for Arab Genomic Studies has reported cases of two Qatari siblings presenting at 12 and 16 years of age with bronchiectasis as an unusual manifestation of homocystinuria.

A Textbook of Clinical Pediatrics describes a nine-year-old girl who was diagnosed as a case of homocystinuria found to have bronchiectasis. This is the first case of homocystinuria presenting as bronchiectasis in India. Bronchiectasis develops due to fibrillin degeneration. Fibrillin is rich in cystine, an end product of homocysteine. Hence, cystine formed in homocystinuria is of poor quality which leads to degenerated fibrillin. Repeated sino-pulmonary infections with the ill-formed fibrillin lead to the structural damage causing bronchiectasis over time. Therefore, bronchiectasis is an unusual and uncommon presenting feature as it is not present at birth and many patients die early due to vascular complications before it develops.

Figure 3 (A and B). High resolution computed tomography of thorax showing bilateral cystic bronchiectasis.
Diagnostic tests include a panel of investigations. The biochemical tests include urine cyanide-nitroprusside to detect increased excretion of sulfhydryl-containing compounds in urine; presence of homocysteine in urine is pathological. Elevated plasma levels of free methionine and homocysteine confirm the diagnosis. Measurement of CBS activity in tissues, e.g. liver biopsy, skin biopsy may be done for research purposes. Contributory diagnostic tests include ophthalmology tests to detect myopia and dislocated lens, and imaging, e.g. radiograph or DEXA scan to detect osteoporosis. Treatment depends on the age at presentation. In a newborn infant, the aim is to prevent affection of various systems and development of normal intelligence by diet modifications and supplementation with pyridoxine and folic acid. Once the complications have occurred management revolves around preventing further escalation and life-threatening complications.7

References