Case Report

Idiopathic Pulmonary Arterial Hypertension in a Young Patient with the Cohen Syndrome

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We admitted a 16-year-old boy with the Cohen syndrome to our institution for increasing dyspnoea. Investigations revealed idiopathic pulmonary hypertension. He was commenced on bosentan and oral anticoagulation and was followed up for nearly 7 years, during which he was readmitted for dynamic measurements of pulmonary artery pressure. Despite initial improvement, the right heart pressures increased again and sildenafil was added. His final hospitalisation was due to increasing breathlessness and episodes of syncope. The addition of prostacyclin conferred no reduction in pulmonary artery pressure. The patient suffered a cardiac arrest and remained intubated for 2 weeks, during which Klebsiella pneumonia and superinfection with the H1N1 swine flu virus occurred. The patient died due to multi-organ failure, nearly 7 years after his initial diagnosis. The Cohen syndrome, its phenotype and clinical findings, and the incidence and treatment of pulmonary hypertension are discussed.

We describe the rare case of a young patient with the Cohen syndrome (an autosomal recessive disorder, MIM 216550) and idiopathic pulmonary hypertension which was diagnosed in our institution. He was followed up for nearly 7 years before dying from worsening heart failure, complicated by pneumonia and superinfection with the H1N1 swine flu virus. To our knowledge, this is the first such case to be described.

Case presentation

A 16-year-old boy with the Cohen syndrome was referred to our institution because of increasing dyspnoea. In the 12 months before admission he had frequent breathlessness on exertion, could not walk more than 100 m outdoors, and exhibited agitation. Some episodes were relieved by squatting, but there was no cyanosis. The boy had suffered from epilepsy since the age of 2 but there were no recent fits or syncopal episodes.

The patient had been born of healthy parents with a normal, full-term delivery. His family lived on an Aegean island, and the boy was diagnosed with the Cohen syndrome at the age of 23 months. He was being followed up in a specialist paediatric unit, where the 8q21.2/8q21.3 translocation has been originally identified.

An older sister, who may have had the same phenotype, had died in childhood after the administration of a general anaesthetic, but no autopsy had been performed.

On clinical examination, the features of the Cohen syndrome were apparent and further confirmed: microcephaly, small cranial base, micrognathia with a short philtrum, prominent incisors, high palate, long fingers, truncal obesity, scissors gait, hypotonia, lateral nystagmus, mild optic atrophy and temporal hetero-
chromia iridis (Figures 1 & 2). The patient had mental retardation with a recorded IQ <50 and a vocabulary of less than 100 words at age 16.

Cardiovascular examination revealed an elevated jugular venous pressure, a prominent parasternal right ventricular heave, an ejection systolic murmur of 3/6 intensity over the pulmonary area, normal arterial blood pressure of 100/65 mmHg, and clear lung fields. The 12-lead electrocardiogram demonstrated characteristic right ventricular hypertrophy and strain with right axis deviation (Figure 3).

Transthoracic and transoesophageal echocardiography showed a normal left ventricle, a dilated right ventricle with preserved systolic function, moderate tricuspid regurgitation with an estimated right ventricular systolic pressure of 90 mmHg, and no intracardiac shunt.

Left and right cardiac catheterization revealed normal coronary arteries, a systolic pulmonary artery pressure (SPAP) of 96 mmHg, and a pulmonary vascular resistance (PVR) of 6.9 Wood units. No shunt or congenital abnormality was detected.

We further investigated the patient with spiral chest CT and a ventilation/perfusion lung scan, both of which were negative for pulmonary embolism. Lung function tests were within normal limits and no restrictive lung pattern was observed. A sleep study revealed no episodes of apnoea. All tests for thrombophilic conditions were negative and the coagulation and immunology screen was normal. No neutropenia was observed. During his hospitalisation, one of the central venous catheterisations resulted in a right-sided pneumothorax, and the parents refused to proceed to a proposed lung biopsy.

The young patient was treated with frusemide, a β-blocker, and sodium valproate for his epilepsy. Oral anticoagulation with a coumarinic agent was started. We concluded that this was a case of idiopathic pulmonary hypertension and initiated treatment with bosentan (Tracleer), a dual endothelin-receptor antagonist, at a starting dose of 62.5 mg bd, progressing to 125 mg bd as his liver function tests remained stable. Attempts to treat him with nebulised prostacyclin failed due to very poor compliance, although he had initially responded to a dynamic trial.

There was some clinical improvement (to New York Heart Association, NYHA class II), and subsequent echocardiograms and readmissions for right heart catheterisation at 6-monthly intervals showed a reduction of the SPAP to 60 mmHg. Four years after initial diagnosis, the patient’s dyspnoea returned to NYHA III and the SPAP to 90 mmHg, so we added sildenafil (Viagra) 25 mg bd, with prompt clinical and haemodynamic improvement. However, 2
years later (6.5 years after initial diagnosis), at the age of 23, he was urgently readmitted due to severe shortness of breath (NYHA IV) and recurrent syncopal episodes which were not attributable to epilepsy. Immediate echocardiography showed a markedly dilated right ventricle, and the patient suffered a cardiac arrest with pulseless electrical activity before a palliative atrial septostomy could be attempted. He was successfully resuscitated, but developed resistant high-grade fever within 24 hours. Urgent right heart catheterisation revealed a SPAP of 98 mmHg and a PVR of 6.5 Wood units. He remained intubated for 2 weeks, during which intravenous prostacyclin, inotropes and nitric oxide were also administered. His condition was further complicated by multi-resistant Klebsiella pneumonia and superinfection with the swine flu H1N1 virus strain on pharyngeal smear polymerase chain reaction. Multiple antibiotics and oseltamivir (Tamiflu) were administered, but uncontrolled sepsis developed and the young man died of multi-organ failure on the 16th day of his last admission, nearly 7 years after the initial diagnosis of idiopathic pulmonary hypertension.

Discussion

We describe a rare case of idiopathic pulmonary arterial hypertension (PH) in a young patient with the Cohen syndrome. To our knowledge, this is the first such fully presented case, with a survival of nearly 7 years from initial diagnosis.

First described by Dr Michael Cohen in 1973, this syndrome constitutes an autosomal recessive disorder (MIM 216550) which is over-represented in Finland. The typical clinical picture includes psychomotor retardation, microcephaly with characteristic facial features, early hypotonia, and retinochoroidal dystrophy. Granulocytopenia has also been described.

More than one genetic abnormality has been described and in some series no chromosomal abnormalities have been found, but the best described is linked to a mutation of the COH1 gene on chromosome 8q, which is common in Finland; this was also the case in our patient. Genetic and clinical heterogeneity can exist among described series.

The cardiovascular system is sometimes involved.

Figure 3. The patient’s 12-lead ECG on admission, showing right ventricular hypertrophy and strain with right axis deviation.
in these patients, with reports of mitral valve prolapse and decreasing left ventricular function with advancing age.\textsuperscript{12,13}

The syndrome manifests differently at different ages and diagnosis remains difficult in infancy. The prognosis is variable and patients can remain in good health into middle age.\textsuperscript{12}

Although pulmonary hypertension has been mentioned in association with this syndrome, no specific case reports have been published in the international literature, and certainly none with such a detailed workup and follow up. The mechanism for pulmonary hypertension is unclear, and although multiple coagulation defects, a restrictive lung pattern, and asplenia have been implicated in some patients,\textsuperscript{14} it appeared to be idiopathic in our case.

These patients are of anaesthetic concern during surgical procedures because of facial asymmetry and mandibular hypoplasia, which can make tracheal intubation difficult.\textsuperscript{15}

The recommended treatment for PH is the use of prostaglandin analogues by continuous intravenous infusion or in nebulised form. Bosentan (Tracleer) is a relatively recently introduced dual endothelin-receptor antagonist which downgrades smooth muscle cell proliferation and constriction of the pulmonary vasculature. Placebo-controlled trials have shown it to improve symptoms and 6-minute walk capacity, while reducing mean pulmonary pressure and vascular resistance and increasing cardiac output. It has been proven to increase 3-year survival in patients with PH, either in isolated use or combined with other agents such as epoprostenol.\textsuperscript{3,4,16} The drug binds to albumin, is metabolised in the liver and excreted in bile, so hepatic enzymes must be closely monitored.

Sildenafil (Viagra), a selective phosphodiesterase-5 inhibitor, has demonstrated favourable effects in PH, with improvement in exercise capacity, haemodynamic parameters, and functional class.\textsuperscript{3,4} Many patients receive combination therapy.

Specialist centres are necessary for the proper evaluation and follow-up of patients with pulmonary hypertension.\textsuperscript{17} Survival rarely exceeds 5 years. In our case, the first such described of idiopathic pulmonary hypertension in the Cohen syndrome, survival was nearly 7 years from diagnosis before the disease’s inexorable progression, the development of resistant pneumonia and superinfection with H1N1 swine flu caused our young patient’s dramatic decline and eventual demise.

We believe that the novel diagnosis of the Cohen syndrome in a young patient should inspire proper cardiac work-up to exclude pulmonary hypertension, which carries an adverse prognosis.

References