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Professional paper

Hereditary Hemorrhagic Telangiectasia or Rendu-Osler-Weber Syndrome in the Same Family

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A B S T R A C T

The authors present the case of three patients from the same family in whom hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome was diagnosed. The disease is rare and occurs with multiple telangiectases of the skin and mucosa, and pulmonary arteriovenous fistulae. The clinical status of our patients included multiple telangiectases of the skin and mucosa, recurrent epistaxis, exertion dyspnea and cyanosis. Polycythemia and hypoxemia were observed in the blood. The clinical status and conventional radiological examination of the thoracic region, with the suspicion of arteriovenous (A-V) fistulae, pointed to HHT. A-V fistulae were confirmed by pulmonary angiography. The pulmonary A-V fistulae were operated in all three patients and diagnosis was confirmed by histopathological examination of the operated samples. Clinical improvement was observed after the operation and cyanosis, dyspnea, hypoxemia and polycythemia disappeared.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome is an autosomal dominant disorder which occurs in families, equally in both sexes. It is characterised by arteriovenous malformations in the form of telangiectases and fistulae in numerous organic systems, which can cause serious complications when located in the lungs, liver or brain. The clinical status varies and symptoms are conditioned by arteriovenous malformations in skin, mucosa and visceral organs. The initial signs of HHT are the appearance of cutaneous telangiectases and recurrent nose bleeding from early childhood. Symptoms of pulmonary arteriovenous fistulae usually occur in adults. Pulmonary arteriovenous fistulae (A-V) can cause hypoxemia and right-left shunt. Diagnosis of pulmonary A-V fistulae is confirmed by pulmonary angiography[1,2].

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The aim of this study was to present three patients with HHT from the same family, and to stress the algorithm of diagnostic procedures in determining the final diagnosis. Although the disease is rare, it should be recognised in practice, final diagnosis confirmed and treatment planned, which is usually surgical.

Patients, Methods and Results

Patient I

T. T., a twenty-three year old unemployed electrician from Zagreb, admitted to the hospital because of cyanosis and exertion dyspnea. Case history showed that as a child he had had frequent epistaxis and bronchitis, and on one occasion pneumonia. Due to the fact that HHT had previously been confirmed in his mother, roentgenograms were performed of the thoracic organs. The findings were normal up until the last one immediately prior to hospitalisation, when lung A-V fistulae were suspected.

On admittance the patient was afebrile, aesthenic constitution, eupneic at rest, cyanotic lips and extremities. He had clubbed fingers and nails which resembled watch glass. Telangiectases could be seen in the nasal mucosa. Marked pectus infundibuliforme on the chest. Normal respiration over the lungs. Cardiac tones clear, rhythm normal, 72/min, RR 110/80 mmHg.

Laboratory findings: haemoglobin in blood (Hb) 176 g/L, haematocrit (Hct) 0.51, erythrocytes (E) 5.4 10^{12}/L. Respiration gases and acidobasal status of arterial blood at rest: hypoxemia, partial oxygen pressure (PO_2) 49 mmHg, normocapnia, normal acidobasal blood status, blood oxygen saturation (SaO_2) 84%. After inhaling high concentrations of oxygen the condition was practically unchanged. Spirometry and lung diffusion capacities were within normal ranges.

The chest X-ray showed oval shadows in the right pulmonary branch which were probably of vascular origin.

Pulmonary angiography showed a small A-V fistula in the posterior basal segment of the left pulmonary lobe and right a very large A-V fistula in the posterior basal segment and another fistula in the middle lobe of the right lung.

Course of disease and treatment: following angiographic confirmation of the diagnosis A-V fistulae, two operations were carried out. During the first operation atypical resection of the middle and lower right lung lobe was performed. Histopathological finding (PHD): fistulae arteriovenosae. During the second operation resection of the posterobasal segment of the left lower lung lobe was performed. PHD: fistulae arteriovenosae.

After the operation signs of right-left shunt, cyanosis and dyspnea disappeared, erythrocytes, haemoglobin and hematocrit normalised, as did gas analysis of arterial blood. The young man has been clinically healthy for four years.

Patient II

One year earlier a diagnosis of HHT, A-V pulmonary fistulae had been confirmed in the young man's forty-two year old mother, F. T. She was admitted to the hospital because of exertion dyspnea, recurrent epistaxis and chest pains which began a few weeks before her admittance. On admittance to hospital the patient was afebrile, eupneic at rest, with cyanotic lips and extremities, and visible telangiectases on the skin of the face and neck, the lips and in the nose. Normal respiration over the lungs, with no murmurs. Cardiac action rhythmic, clear tones, with no murmurs, RR 130/90 mmHg.

Laboratory findings: haemoglobin in blood (HgB) 170 g/L, haematocrit (Hct) 0.50, erythrocytes (E) 5.5 10^{9}/L. Respiratory gases and acidobasal status of ar-

terial blood at rest: hypoxemia, partial oxygen pressure (PO_2) 49 mmHg, hypocapnia, partial CO pressure (PCO_2) 33.2 mmHg, normal acidobasal blood status, blood oxygen saturation (SO_2) 86.6%. After inhaling high concentrations of oxygen the condition was unchanged. Spirometry and lung diffusion capacity: normal.

Chest radiography showed a round lesion on the right of the parenchyma (Figure 1) diameter 2 to 4 cm, with characteristic vascular anomalies.

Pulmonary angiography: A-V fistulae in the upper, middle and lower lobes of the right lung (Figure 2).

Course of disease and treatment: following angiography and confirmation of the diagnosis pulmonary A-V fistulae, right lower lobectomy was performed and obliteration by suturing the other three A-V fistulae in the right lower and middle lobe.

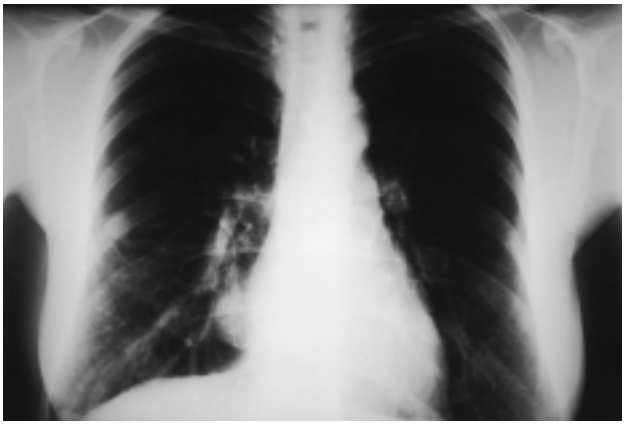

Fig. 1. Plain chest radiograph showing multiple A-V fistulae in the parenchyma of the right lung.

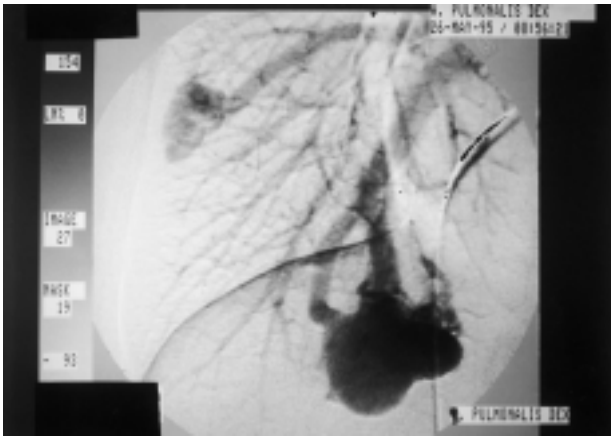

Fig. 2. Pulmonary angiography – A-V fistuale can be seen in the upper, middle and lower lobes of the right lung.

Histopathological finding (PHD) of the right lower lobe: fistulae arterio venosae.

Post-operative course normal. Signs of right-left shunt disappeared after the operation, and erythrocytes, haematocrit, haemoglobin and partial oxygen pressure in arterial blood (pO_2) normalised. The mother has been clinically healthy for three years.

Patient III

S. M., an eighteen year old nephew of F. T. from Vinkovci, in whom an oval shadow, indicating vascular aetiology, was detected on a systematic chest X-ray, was admitted to the Hospital for Lung Tuberculosis and Pulmonary Diseases in Children and Adolescents, Srebrenjak, Zagreb.

Laboratory findings: haemoglobin in blood (HgB) 185 g/L, erythrocytes 5.42 10^{12}/L.

Spirometry and arterial blood gas analysis: normal. Chest radiography showed a homogenous oval shadow in the area of the lingule, sharply defined and with drainage in the direction of the hilus.

Course of disease and treatment: lingule resection was performed and the surface ateriovenous fistulae in the VI projection of the segment ligated.

Histopathological finding (PHD): fistulae arteriovenosae. Operative and postoperative course normal. The patient has been clinically healthy for 14 years.

Discussion

HHT is a rare, hereditary disease, characterised by anomalies of the blood vessels in the mucosa of the nose, skin, lungs, brain and intestinal tract, which can be clinically manifest from early childhood to late adulthood, usually up to 40 years[3,4]. In our patients it was clinically manifested in adolescence and mature age. HHT occurs in many ethnic groups, and studies on prevalence indicate, at least in the investigated populations[5–9] that HHT is more frequent than was earlier thought (Table 1). The frequency of HHT in Croatia has not been investigated and these are, therefore, the first documented data on HHT in our population.

In 1896 Rendu first described a combination of hereditary epistaxis and telangiectasia[10]. Later studies were published by Osler[11] and Weber[12], and a derivation of hereditary hemorrhagic telangiectasia was given by Hanes in 1909, confirming the three components which define this disease[13].

TABLE 1
INCIDENCE OF HHT IN SOME GEOGRAPHICAL REGIONS

Geographical region	HHT incidence
France – Ain	1/2351
Danmark – islands Funen	1/3500
Netherlands – islands Leeward	1/5155
USA – Vermont	1/16500
North England	1/39216

Clinical criteria for diagnosis of hereditary hemorrhagic telangiectasia is the presence of at least two of the following criteria: recurrent epistaxis, telangiectasia other than in the nasal mucosa, evidence of autosomal dominant inheritance, involvement of the internal organs[14].

Our patients were all members of the same family. They suffered from recurrent epistaxis, telangiectasia in the nasal mucosa and skin and involvement of the internal organs in the form of pulmonary A-V fistulae. Clinically manifest hereditary hemorrhagic telangiectasia occurs because of abnormality in the vascular structures. Smaller anomalies are usually described as telangiectasia and lar-

ger as A-V fistulae. However, there is no distinct border between them[15]. Telangiectases are focal dilatation of postcapillary venules, which occur most frequently in the nasal mucosa, on the lips and facial skin most frequently in early childhood. In our patients they were observed on the lips, nasal mucosa and the facial skin in adolescence and at a mature age. Telangiectases cause frequent bleeding from the mucosa, particularly of the nose, as was the case in our patients, and very often from the digestive tract, particularly at a mature age. It is treated surgically, by laser or hormonal therapy[16,17]. In our patients no treatment was carried out of the observed telangiectases. Larger malformations, which consist of directly connected arteries and veins are called A-V fistulae. They frequently appear in the lungs, are usually multiple and restricted to one lung lobe and are most frequent in the lower lobes. Although they are inherited and can be present at birth, pulmonary A-V fistulae are rarely clinically manifest before adulthood, after the blood vessels have been exposed to increased pressure for several decades[18,19]. Our patients had multiple pulmonary A-V fistulae, localised mainly in the lower lung lobes and clinically manifest in adulthood. Approximately 60% of persons with pulmonary A-V fistulae have HHT, and 5–15% of those with HHT have pulmonary A-V fistulae[20]. All three of our patients with pulmonary A-V fistulae had HHT. Pathologic communications between the arteries and veins of the lungs lead to right-left shunt with reduction of part of the blood from the circulation, which, particularly when multiple, leads to dyspnea, cyanosis and polycythemia[21], as was the case in our patients. A continuous murmur can often be heard over A-V fistulae, although this was not the case in our patients. The blood count shows polycythemia, hypoxemia, which is more marked during exercise and which does not change after the oxygen test, which was marked in our patients. Roentgenograms of the thoracic organs usually shows single or multiple, homogenous, round, well circumscribed shadows in one of the lower pulmonary lobes[22–26]. In our two male patients roentgenograms of the thoracic organs showed single, oval, sharply circumscribed shadows in the lower pulmonary lobes, and in our female patient multiple, round, sharply circumscribed shadows in the right lower pulmonary lobe. In the diagnostics of pulmonary A-V fistulae radionuclide perfusion lung scintography, echocardiography and computed tomography and magnetic resonance, according to data from literature in typical forms show A-V malformations on the supplying and draining blood vessels[27–33].

The final diagnosis is determined by pulmonary angiography[34], with which we confirmed the diagnosis of pulmonary A-V fistules in two of our patients.

Complications of A-V fistulae can be local: rupture or infection of the fistulae, or general: embolus, thrombosis, brain abscess and death[35]. Occasionally the first manifestations of pulmonary A-V fistulae are the neurological consequence of stroke and abscess, which occur because of right-left shunt with facilitated passage of septic and blood clots[36,37]. Our patients had none of the above complications.

Successful therapy for non-diffusive fistulae is surgical; removal of the diseased part of the lung, which was performed in all three of our patients. Diffuse A-V fistulae are treated by embolisation of the larger fistulae, primarily for prevention of paradoxical emboli[38,39]. Successful operation and embolisation lead to a disappearance of right-left shunt and its clinical signs[40,41]. This was the case in our patients, in whom cyanosis, dyspnea and polyglobulia disappeared after the operation and all signs of

right-left shunt. As unrecognised HHT and A-V fistulae can lead to unexpected serious illness and death, it is important for diseased persons and those at risk of HHT should be examined (chest X-ray, CT, oximetry and if necessary CT of the brain) at puberty, the end of adolescence and women prior to pregnancy[42–44]. In the near future routine genetic tests for HHT and relevant therapy are envisaged[45,46].

No tests were carried out in other members of the family for HHT, after the discovery of pulmonary A-V fistulae in the first patient, who also had recurrent apistaxis because of telangiectases in the nasal mucosa, which satisfied two clinical criteria for a diagnosis of HHT[14]. After pulmonary A-V fistulae had been confirmed in another member of the family HHT was diagnosed in both patients and later in a third member of the family. The first patient, apart from apistaxis, had no clinical disorders, and the disease was detected by chance in adolescence. The other two patients had dyspnea, cyanosis and recurrent epistaxis. Roentgenograms of the thoracic organs showed round and oval, sharply circumscribed shadows. Diagnosis of pulmonary A-V fistulae was confirmed by pulmonary angiography and histopathologically in the lung tissue during the operation. Since the successful operations the patients have been clinically healthy.

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HEREDITARNA HEMORAGIČNA TELEANGIEKTAZIJA ILI RENDU-OSLER-WEBEROVA BOLEST U JEDNOJ PORODICI

S A Ž E T A K

Autori prikazuju tri porodično povezana bolesnika u kojih je dokazana hereditarna hemoragična teleangiektazija (HHT) ili Rendu-Osler-Weberova bolest. Bolest je rijetka i javlja se multiplim teleangiektazijama kože i sluznica te plućnim arterijsko-venskim fistulama. Našim je bolesnicima u kliničkom statusu zajedničko: multiple teteangiektazije kože i sluznica, učestale epistakse, dispneja u naporu i cijanoza. U krvi je uočena policitemija i hipoksemija. Takva klinička slika i konvencionalna radiološka obrada torakalne regije-sumnja na arterijsko-venske (A-V) fistule upućivale su na HHT. A-V fistule dokazane su plućnom angiografijom. U svo troje bolesnika su operirane plućne A-V fistule i dijagnoza je potvrđena patohistološkim pregledom operacijskih uzoraka. Nakon operacije uslijedilo je kliničko poboljšanja. Nestala je cijanoza, dispneja, hipoksemija i policitemija.