CASE REPORT

At high altitude in the Netherlands: secondary erythrocytosis due to HB-Malmö

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SUMMARY

We describe two patients, a father and a son, presenting with erythrocytosis. Evaluation showed no pulmonal or cardial disorders. Owing to an elevated erythropoietin level after phlebotomy, a physiological secondary polycythaemia was suspected. A haemoglobin electrophoresis showed that our patients have a haemoglobinopathy with high affinity for oxygen, called Hb-Malmö (exon 3: c.294 C>G p.His98Gln). Hb-Malmö is a congenital disorder located on a gene at chromosome 11, in the B-chain on codon 97, decoding the α-subunit and β-subunit of the haemoglobin. Through a mutation (CAC→CAG), histidine is replaced by glutamine. The mutation causes a disorder in the connection between the α1-subunit and β2-subunit of the haemoglobin structure. These connections are important sites for binding oxygen. Mutated haemoglobin has a preference for an oxygenated status, which implicates that there is an increased binding and decreased release of oxygen. To compensate, there will be an erythrocytosis to transport sufficient oxygen to the peripheral tissues.

BACKGROUND

We think this case is important because HB-Malmö is a rare disease, but it must also be considered in patients with erythrocytosis. We showed in our patient that because of the high affinity of haemoglobin for oxygen, people with HB-Malmö can develop lactic acidosis in exercise. And we think our case also shows that re-evaluation of a clinical problem, former diagnosed as idiopathic, can expose a new diagnosis.

CASE PRESENTATION

A 68-year-old patient, with a medical history of a pulmonary embolism 10 years ago, presented at the outpatient clinic with atypical chest pain and polyglobulia. He quit smoking 5 years ago (after 40 pack-years). On physical examination, we found normal blood pressure and oxygen saturation. He had some blushes on his cheeks. There were no signs of dehydration. Cardial and pulmonal examinations were normal.

INVESTIGATIONS

Results of the blood examination are given in table 1. In conclusion, there was an absolute erythrocytosis. In retrospect, our patient had an erythrocytosis since 1997, when his first blood samples were documented. Previously, he was diagnosed at a university hospital with idiopathic erythrocytosis and was treated with periodic phlebotomy.

Table 1 Laboratory values of our patient

	Normal	Patient
Haemoglobin (mmol/L)	8.5–11.0	13.7
Haematocrit (L/L)	0.4–0.5	0.67
MCV (fL)	80–100	92
Red blood cell count (10^{12}/L)	4.5–5.5	6.92
Leucocytes (10^9/L)	4.0–10.0	6.9
Platelets (10^9/L)	150–400	166
Erythropoietin (u/L)	3.0–34.0	26.3
JAK2-V617F mutation		Negative
HbCO		Normal

HbCO, carbon monoxide; MCV, mean corpuscular volume.

We performed a new analysis of the erythrocytosis in our patient. Lung function testing showed normal oxygenation and ventilation and ruled out obstructive and restrictive lung diseases. Cardiac ultrasound showed a good left ventricular ejection fraction and no systolic or diastolic dysfunction.

The patient did not have a history of carbon monoxide exposition or altitude training. Radiological investigations of the abdomen, cerebrum and renal arteries were normal. Methaemoglobin values were not elevated. A JAK2-V617F mutation was excluded and the erythropoietin level was at the upper limit of normal.

Bone marrow puncture showed an increased erythropoiesis with normal morphology and an erythropoietin-dependent erythroid clonic growth. Cytogenetics showed a normal male karyotype without cloned chromosomal disorders.

After phlebotomy, the erythropoietin level increased, matching physiological secondary polycythaemia. The p50 of the oxygen dissociation curve by the algorithm of Siggaard-Andersen showed a left shift, which can be seen in disorders of the haemoglobin. Arterial blood gas analysis confirmed this suspicion. As shown in table 2, after exercise, our patient not only had an elevated oxygen tension, but also lactic acidosis and therefore hypoxia at the tissue level. A 2,3 diphosphoglycerate (DPG) deficiency was ruled out.

A haemoglobin electrophoresis (high-pressure liquid chromatography) showed that our patient has a haemoglobinopathy with high affinity for oxygen, called Hb-Malmö (exon 3: c.294 C>G p.His98Gln).

DIFFERENTIAL DIAGNOSIS

Elevated haemoglobin and red blood cell count, called erythrocytosis, is frequently diagnosed in a

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Table 2 Values of oxygen saturation, pH, bicarbonate and lactate in rest and after exercise in our patient

	Normal	Rest	Exercise
pH	7.35–7.45	7.43	7.24
pO_2 (kPa)	10.0–13.3	17.8	16.7
pCO_2 (kPa)	4.7–6.4	4.5	3.7
O_2 saturation (%)	96–100	100	99
Bicarbonate (mmol/L)	22.0–29.0	22.3	11.4
Base-excess	−2–2	−0.6	−14.9
Lactate (mmol/L)	0.6–2.4	1.4	18

patient when blood investigation is performed for other reasons. Erythrocytosis can be due to many causes.

Dehydration can cause a relative erythrocytosis.

Otherwise, in the absence of dehydration, there is an absolute erythrocytosis. This is mostly caused secondarily by other disorders, like cardial or pulmonal diseases. Disorders in the development of red blood cells in bone marrow are primary causes of erythrocytosis. Table 3 shows all causes of an elevated red blood cell count.

OUTCOME AND FOLLOW-UP

As his 40-year-old son, without any medical history, had tiredness, painful muscles and shortness of breath, we performed a physical examination and laboratory investigation. The results showed an elevated haemoglobin as well as an increased amount of erythrocytes. Based on the results, a haemoglobin electrophoresis (high-pressure liquid chromatography) was performed that also showed Hb-Malmö.

Both patients started with regular phlebotomy, whereupon their haemoglobin level normalised.

DISCUSSION

Hb-Malmö was first described in 1970 by Lorkin and Lehmann[2] in four generations of a Swedish family with erythrocytosis.[3] It is an autosomal dominant congenital disorder located on a gene at chromosome 11, in the B-chain on codon 97, decoding the α-subunit and β-subunit of the haemoglobin.[3] Two different mutations have been described (CAC→CAA and CAC→CAG) by which histidine is replaced by glutamine.[4] This change in amino acid causes a disorder in the connection between the α1-subunit and β2-subunit of the haemoglobin structure. These connections are important sites for binding oxygen. Mutated haemoglobin has a preference for an oxygenated status, a high affinity for oxygen, which implicates that there is an increased binding and decreased release of oxygen. To compensate, there will be renal impairment of erythropoietin production, by which the bone marrow is stimulated to produce more red blood cells to transport sufficient oxygen to the peripheral tissues.[5] So there is a secondary physiological erythrocytosis.

Over 100 variants of haemoglobin with high affinity for oxygen are described so far.[6 7] Like Hb-Malmö, there are other haemoglobinopathies (Hb San Diego, Hb Johnstown, and Hb Columbia-Missouri) with high affinity for oxygen due to changes in the contact between α1-subunit and β2-subunit. Other haemoglobinopathies with high affinity for oxygen are due to changes in 2,3DPG, in the contact cavity to the haemgroup and the contact between α1-subunit and β1-subunit.[7]

In the international literature, 10 families or single cases have been described with Hb-Malmö.[2 4 6 7–15]

Clinical symptoms of patients with Hb-Malmö are non-specific and most patients are asymptomatic. Dyspnoea, tiredness, painful muscles, blushes and chest pain are frequent symptoms. Most symptoms can be explained by the decreased release of oxygen by haemoglobin.

Blushes are explained by the elevated blood viscosity caused by more red blood cells.

Blood levels of haemoglobin and haematocrit vary between the different cases from normal to extreme elevated levels. Haematocrit levels of patients are usually above 0.60.[8]

So our patients would be the 11th report of different families with Hb-Malmö. Unfortunately, our 63-year-old patient had a bad relationship with his sister living on the other side of the Netherlands. So we wrote her a letter for more information about her medical history. She responded that she had 'the Swedish disease'. It appeared that her family was reported by Giordano[14] in 1996 and so our patients are a part of this same family.

Table 3 Causes of erythrocytosis, divided by relative and absolute causes

Relative			Dehydration Smoking
Absolute	Primary		Polycythaemia vera Primary familiar congenital polycythaemia Idiopathic erythrocytosis
	Secondary	Physiological	Pulmonal diseases Congenital heart diseases (shunting) Intoxications High-affinity haemoglobin High altitude
		Pathophysiological	Kidney diseases Liver diseases Tumours producing EPO Endocrine disorders Medication Dysregulation of oxygen detection

The absolute causes are also divided into primary and secondary causes.
EPO, erythropoietin.[1]

Learning points

- HB-Malmö is a rare disease, but must be considered in patients with erythrocytosis.
- Owing to the high affinity of haemoglobin for oxygen, people with HB-Malmö can develop lactic acidosis in exercise.
- Re-evaluation of a clinical problem, formerly diagnosed as idiopathic, can expose a new diagnosis.

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