ERYTHROPOIETIN-DEPENDENT ANAEMIA: A POSSIBLE COMPLICATION OF DIABETIC NEUROPATHY

S. HADJADJ (1), F. TORREMOCHA (1), A. FANELLI (1), A. BRIZARD (2), M. BAUWENS (3), R. MARÉCHAUD (1)

SUMMARY - We report the case of a 52-year-old woman with long-term type 1 diabetes mellitus, complicated with proliferative retinopathy, autonomic neuropathy and microalbuminuria and moderate renal failure. A normochromic, normocytic aregenerative anaemia had been diagnosed for three years. Clinical and biological investigations for the aetiology of anaemia remained normal or negative. Anaemia was associated with a concentration of erythropoietin (EPO) in the normal range, but inappropriately low regarding anaemia. Treatment with recombinant EPO induced a rapid increase in haemoglobin level and improved the patient’s quality of life. The role of diabetic neuropathy in the genesis of anaemia, in conjunction with a modest renal impairment is discussed.

Key-words: anaemia, autonomic neuropathy, diabetes, erythropoietin.

RE´ SUME´ - Anémie dépendant de l’érythropoïétine : une complica-
tion possible de la neuropathie diabétique.
Nous rapportons le cas d’une femme de 52 ans avec un diabète de type 1 de longue durée d’évolution, compliqué de rétinopathie proliférative, de neuropathie autonome et de microalbuminurie avec insuffisance rénale modérée. Une anémie normochrome, normocytaire, arégénérative évo-
luée depuis 3 ans. Les examens cliniques et biologiques cherchant l’éti-
ologie de cette anémie sont normaux ou négatifs. L’anémie s’associe à une concentration d’érythropoïétine (EPO) dans les limites de la normale, mais basse de façon inappropriée en regard de l’anémie. Un traitement
par EPO recombinante induit une élévation rapide de la concentration
d’hémoglobine et améliore la qualité de vie de la patiente. Le rôle de la neuropathie diabétique, en conjonction avec une dégradation minime de la fonction rénale, est discuté pour le développement de l’anémie.

Mots-clés : anémie, neuropathie autonome, diabète, érythropoïétine.
Erythropoietin (EPO) is a potent stimulator of erythropoiesis, produced in the kidney [1]. Renal failure is the major cause of EPO-dependent anaemia. Anaemia has also been described in patients with neurologic conditions involving the autonomic nervous system, such as multiple system atrophy or pure autonomic failure [2, 3]. We report the case of a 52-year old type 1 diabetes patient with severe diabetic neuropathy suffering from chronic anaemia associated with inappropriately low EPO concentration.

## CASE REPORT

A 49-year old type 1 diabetes woman was referred in our department for a left heel wound in 1997. She had a history of hysterectomy for fibromyoma and of type 1 diabetes mellitus diagnosed for 19 years. Diabetes was associated with vitiligo and auto-immune hypothyroidism, and was mainly complicated with severe proliferative retinopathy. On admission, clinical examination mainly revealed asthenia, body weight of 55 Kg and height of 1.67 m. She had diabetic neuropathy with peripheral neuropathy (heel wound, neurosensory impairment assessed by monofilament test, abolished lower limb tendon reflexes) and autonomic neuropathy consisting in diarhoea, severe symptomatic postural hypotension: acouphenes, blood pressure falling from 159/66 to 82/39 mmHg, with no change in heart rate at 92 bpm. Fludrocortisone (100 µg/day) was ineffective on postural hypotension. On ECG, deep breathing (5 sec inspiration/5 sec expiration for 1 minute) induced no variation in heart rate. She also had diabetic nephropathy with microalbuminuria (median urinary albumin excretion: 58 mg/l) and normal plasma creatinine: 112 µmol/l, corresponding to a creatinine clearance of 45 ml/mn, according to Cockroft formula. Ultrasonography revealed left and right normal-sized kidneys: 115 × 47 mm and 123 × 54 mm, respectively. Treatment consisted in captopril (100 mg/day), a 4-insulin injection regimen, resulting in poor metabolic control (HbA1c: 9.2%, Normal Value (NV): 4-6), and L-Thyroxine (150 µg/day) with adequate dosing (TSH: 0.43 mUI/l, NV: 0.2-4).

Biological data revealed a normocytic, normochromic anaemia: haemoglobin 9.7 g/dl, haematocrit 20.9%, mean cell volume 88.7 fl, reticulocytes 70 000/ mm3 with normal white cell and platelet count, respectively: 6 100/mm3 and 199 000/mm3. Serum iron concentration was normal: 13 µmol/l (NV: 12-30), with increased iron binding capacity: 66 µmol/l (NV: 20-60). Ferritin and haptoglobin were normal at 105 µg/l and 0.68 g/l (NV: 30-230 and 0.34-2.00) respectively.

Aetiological investigations were all negative or normal including colonoscopy and eso-gastro-duodenoscopy, Coombs’ test, vitamine B12 and folate levels, HIV serology, bone marrow aspirate, calcium and phosphorus plasma levels.

Anaemia was unaffected by a 4 months iron treatment, or by the switch from captopril to slow release verapamil (240 mg/day). Postural hypotension did not resolve after changing anti-hypertensive therapy.

Haemoglobin level remained unchanged, ranging between 9.4 and 10.2 g/dl. Erythropoietin concentration was dosed in the morning (7.00 am) using a commercial kit (Quantikine IVD EPO ELISA, R & D Systems, Minneapolis, MN, USA). EPO was inappropriately low at 3.6 mUI/ml (NV: 3.3-16.6) regarding haemoglobin level (9.8 g/dl). The patient was put on recombinant-EPO therapy (2 000 IU, twice a week) until haemoglobin reached the concentration of 12 g/dl. The correction of anaemia after 2 months of EPO treatment resulted in a rapid healing of the heel wound, an improved well-being, with no asthenia, and no change in diabetic nephropathy (creatinine: 107 µmol/l, and urinary albumin concentration: 28 mg/l). Postural hypotension and deep breathing test were still abnormal.

## DISCUSSION

Normochromic, normocytic anaemia was diagnosed in a long-term type 1 diabetes woman, with microvascular complications. The treatment with recombinant EPO was supported by the positive evolution of the chronic wound, and the dramatic improvement in well-being of the patient, without running the risk of blood transfusion.

The aetiology of anaemia is questionable. The aetiological investigations allowed to rule out many diagnostic hypotheses, particularly including an iron deficiency, as iron and ferritin levels were normal, and iron therapy was ineffective. The causality of angiotensin converting enzyme inhibitor was possible, as it has been shown to inhibit red cell precursor growth [4] or even lower EPO concentration [5]. The lack of correction of anaemia after captopril was stopped ruled out the hypothesis of an adverse effect of this treatment. The adequate L-Thyroxine dosing also ruled out the possibility of hypothyroidism-induced anaemia.

The anaemia was associated with a concentration of erythropoietin (EPO) in the normal range, but inappropriately low regarding anaemia. We used the data published by Winkler et al. to assess the level of EPO predicted by Hb level, as we used the same analytical method [6]. In our patient, EPO was twice as low as expected, showing a blunted EPO response to anaemia.

EPO-dependent anaemia complicating type 1 diabetes was first described in 1995 [7]. Rare cases were described later [6, 8, 9]. Anaemia was not associated with markedly impaired renal function, but autonomic nervous function was severely affected. The responsi-
bility of diabetic autonomic neuropathy in the inappropriately low EPO response is possible. This hypothesis is supported by animal studies showing that the stimulation of beta 2 adreno-receptors increase EPO production [10]. It is also supported by the occurrence of anaemia in human diseases involving the autonomic nervous system: multiple system atrophy and pure autonomic failure [2, 3]. Diabetic neuropathy was present in our patient, with evidence of autonomic dysfunction on deep-breathing test and severe postural hypotension.

Alternate hypotheses could be discussed: an impairment of oxygen sensing receptor could lead to an absence of EPO gene stimulation, resulting in an EPO-dependent anaemia; in the context of our patient having an auto-immune disease (vitiligo, thyroiditis and type 1 diabetes), one can also speculate on the presence of an antibody directed against EPO or EPO receptor, or affecting intracellular signalling of EPO in erythroblasts.

The degree of diabetic nephropathy we described in our patient is not generally associated with an inappropriately low EPO concentration [11]. However, renal function was not completely normal in this case, as plasma creatinine corresponded to a creatinine clearance of 45 ml/min. The conjunction of mild renal impairement with severe autonomic dysfunction might be involved in the genesis of EPO blunted response to anaemia. This should be evaluated in patients with normal renal function and autonomic dysfunction.

REFERENCES