Autonomic dysfunction and anemia in neurologic disorders

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Received 30 April 1996; revised 10 June 1996; accepted 10 June 1996

Abstract

The effect of autonomic dysfunctions on anemia in various neurological disorders, such as familial amyloidotic polyneuropathy (FAP) Type I, pandysautonomia, and Shy–Drager syndrome was examined. As a control, hemograms of patients with amyotrophic lateral sclerosis (ALS), which is known to be free from autonomic dysfunction, was compared with patients with the above neurological disorders. FAP and pandysautonomia patients showed significant anemia comparable with the severity of the autonomic dysfunctions. Shy–Drager patients exhibited mild anemia. However, in ALS patients, no such anemia was recognized at all even in the end stage of this disease. In pandysautonomia patients, hypoplastic bone marrow was recognized, which was quite consistent with the data previously reported in FAP patients. Human recombinant erythropoietin improved orthostatic hypotension as well as anemia in 4 FAP patients. These results suggest that autonomic dysfunction may be deeply connected with erythropoiesis.

Keywords: Anemia; Orthostatic hypotension; Familial amyloidotic polyneuropathy; Pandysautonomia; Shy–Drager syndrome; Human recombinant erythropoietin

1. Introduction

Analysis of anemia is one of the most well examined research fields among medical science because anemia is induced by various factors and is found in various pathologic conditions. It is well known that, since autonomic nerves dominate in the bone marrow itself and in its surrounding tissues [9], dysfunction of these nerves may modulate the production of blood cells in the bone marrow [6–8]. Takaku et al. reported that the reticulocyte response to acute blood letting was significantly diminished in rats when their kidneys were functionally denervated [19]. Intravenous administration of the α-adrenergic receptor agonist increased plasma concentration of an erythropoietin-like factor in the rabbit [10,11]. On the contrary, there is a report that α-adrenergic blockers blunted the erythropoietin response to hypoxia [21]. Despite several investigations on erythropoiesis and nerve functions in animals, few analyses have been performed on erythropoiesis of patients with autonomic dysfunction. Biaggioni et al. reported on the anemia of primary autonomic failure [8], but the decrease of plasma hemoglobin (Hb) levels were very mild.

We have recently reported that significant anemia was recognized in patients with familial amyloidotic polyneuropathy (FAP) Type I (Met30) and severity of anemia was correlated with the progression of the disease [5]. FAP Type I, which is inherited in an autosomal dominant manner, is associated with a sensory dominant mixed type polyneuropathy that starts in the lower limbs [2–4]. The symptoms appear between the ages of 20 and 45 yr (mean: 34.6 ± 5.8 yr) [21]. Autonomic dysfunctions, such as alternating diarrhea and constipation, urinary disturbances, impotence, orthostatic hypotension, and hypoglycemia, are the first symptoms followed by sensory disturbances [1]. Since no amyloid deposition was recognized in the biopsied and autopsied bone marrow materials, this anemia may be induced by the altered condition of surrounding tissues, such as nerves and vessels [5].
We examined the effect of autonomic dysfunctions on anemia in various neurological disorders, such as FAP Type I, pandysautonomia, and Shy–Drager syndrome. As the disease control, hemograms of patients with amyotrophic lateral sclerosis (ALS), which is known to be free from autonomic dysfunction, were compared with those of patients with autonomic disorders. The outcome of the effect of erythropoietin on anemia and the changes in clinical findings were also described in FAP patients.

2. Patients and methods

2.1. Subjects

We examined 26 FAP patients (28–71 yr, 14 males, 12 females, average: 38.3 ± 8.3 yr), 4 with pandysautonomia (a 38-yr-old male, 3 females: 11, 40 and 41 yr old), 9 Shy–Drager (48–76 yr, 8 males, 1 female, average: 56.8 ± 7.6 yr), and 21 ALS (45–76 yr, 12 males, 9 females, average: 52.5 ± 8.9 yr) referred to Kumamoto University School of Medicine and Arao City Hospital. None of the patients evidenced bleeding disorders, overt endocrinological dysfunction, or hepatic insufficiency. Patients with known causes of anemia, such as iron deficiency and megaloblastic anemia or concurrent illness known to cause the anemia of chronic disease were also excluded from this study.

2.2. Bone marrow aspiration

In 2 pandysautonomia patients, bone marrow aspiration was performed under local xylocaine anesthesia. The reference values of differential counts of bone marrow aspirates were used as described in [20].

2.3. Definition of anemia

We used the WHO definition of anemia [12], Hb < 12.0 g/dl for women and < 13.0 g/dl for men.

2.4. Autonomic dysfunction score

To evaluate the autonomic dysfunction, the following scores were given to the patients examined. Since it is impossible to evaluate the sexual autonomic dysfunction in the female, evaluation of impotence was omitted.

- Diarrhea (0: negative, 2: alternation of constipation and diarrhea, 4: regular diarrhea, 6: severe diarrhea).
- Orthostatic hypotension (0: negative, 2: systolic blood pressure: 0–20 mmHg decrease, 4: more than 20 mmHg decrease, 6: severe with faintness).
- Urinary incontinence (0: negative, 2: occasional urine loss, 4: mild, 6: permanent incontinence or retention of urine).
- Dry eye (0: negative, 3: positive).

Dry mouth (0: negative, 3: positive).

Impairment of sweating (0: negative, 3: positive).

2.5. Statistical analysis

Statistical evaluation was performed by the paired t-test. A p value < 0.05 was taken to be statistically significant.

3. Results

3.1. Anemia in patients with autonomic dysfunction

Fig. 1 shows the Hb levels in patients with FAP, pandysautonomia, Shy–Drager disease, and ALS. In patients with FAP and pandysautonomia, Hb levels were significantly lower than those in ALS patients. Those levels in Shy–Drager patients were slightly decreased and slight statistical significance was in compared with those in ALS patients. Correlation between Hb levels and the degree of autonomic dysfunction in all patients examined are demonstrated in Fig. 2. Significant correlation between the 2 factors was observed in FAP, pandysautonomia, and Shy–Drager patients, but not in ALS patients.

3.2. Findings of bone marrow aspiration in pandysautonomia patients

Bone marrow aspiration was also performed in 2 pandysautonomia patients (a 40-yr-old and a 41-yr-old female). Both patients showed low total cell count with
high myelocytic series/erythrocytic series ratio. The M/E ratio was also very high in both patients (7.41 and 7.92, respectively). The reactive abundance of reticulocytes in the peripheral blood of these patients was low (1.12% and 1.29%, respectively).

3.3. Effect of human recombinant erythropoietin on anemia

Despite the continuous administration of iron, blood Hb levels did not increase and plasma iron levels were unchanged in FAP patients. Furthermore, repeated administration of vitamin B₁₂, folate, and iron had no effect on anemia in FAP patients. Recombinant human erythropoietin was administered to 4 FAP patients with severe anemia for 4–12 weeks. A 50-yr-old female received 9000 units of erythropoietin intravenously 3 times weekly for 2 weeks without iron supplementation (300 mg/day), and then 6000 units twice weekly for another 2 weeks with 200 mg/day of iron. Her blood hemoglobin levels were elevated from 7.6 to 11.7 g/dl, and was elevated from 24.0 to 36.3%. After that, she received 3000 units of erythropoietin once weekly for 12 months and her plasma Hb levels were maintained at 8.9–10.0 g/dl. Therapy had an unexpected effect on the systolic blood pressure, which rose from the 80 to 100 mmHg range to the 120 to 140 mmHg range. The frequency of episodes of orthostatic hypotension was significantly reduced. Plasma Hb levels of a 26, a 36 and a 49-yr-old male FAP patient were also increased from 8.5 to 10.4 g/dl and systolic blood pressure increased from 70–100 to 110–130 mmHg after intravenous administration of 3000 units of erythropoietin weekly (Table 1). The frequency of episodes of orthostatic hypotension was also significantly reduced. The 26-yr-old male showed no orthostatic hypotension at all after 6 week of erythropoietin administration. Other neurological findings did not change at all during or after administration of erythropoietin.

4. Discussion

We demonstrated in this report that the degree of anemia is correlated with that of autonomic dysfunction. As shown in Figs. 1 and 2, patients with FAP and pandysautonomia revealed more severe anemia than that in Shy–Drager syndrome [8]. This may be partially because Shy–Drager patients showed milder autonomic dysfunction than in FAP and pandysautonomia patients: gastrointestinal symptoms and glandular autonomic dysfunctions, such as dry mouth and dry eye, are also more often involved in FAP and pandysautonomia patients than in Shy–Drager syndrome patients [9,18]. In contrast, ALS patients exhibited normal hemoglobin levels even at the end stage of this disease. In ALS patients, because of hypoxemia, some compensatory mechanism may occur even in the emaciated state.
Although we did not perform bone marrow analysis in Shy–Drager syndrome patients because of ethical reason, bone marrow aspiration in pandysautonomia patients revealed hypoplastic bone marrow. This data was quite consistent with that previously reported [1]. Asahara et al. reported that 83% of the FAP patients showed hypoplastic bone marrow [5]. Although in all the cases, significant amyloid deposition was apparent in the surrounding stroma and vessels, there was no amyloid deposition in the bone marrow itself. These results suggest that anemia found in most of the patients with severe autonomic dysfunction may be the result from hypoproliferative bone marrow.

We also examined the Hb levels in patients with severe diarrhea, such as Crohn disease and ulcerative colitis. Although iron deficiency anemia was found 12% and 9% of patients with Crohn disease and ulcerative colitis, respectively, no hypoproliferative anemia was recognized in these patients (data not shown). This result suggests that, although poor nutrition often occurs in FAP and pandysautonomia patients, it may not lead to hypoproliferative anemia found in patients with autonomic dysfunction. In fact, despite the continuous administration of iron, blood Hb levels did not increase in FAP patients. Furthermore, repeated administration of vitamin B₁₂ and folate had no effect on anemia in FAP patients.

Since serum erythropoietin levels of FAP patients did not increase despite severe anemia (8.5 ± 3.6 ng/l, n = 10), recombinant human erythropoietin, which has been widely used for anemic diseases [13,16], was administered to 4 FAP patients with severe anemia. Anemia was improved after repeated administration of erythropoietin and the frequency of episodes of orthostatic hypotension was significantly reduced because of the effect of erythropoietin. Other neurological findings did not change at all during or after administration of erythropoietin. Since erythropoietin would correct the deficit in red cell mass without causing hypervolemia [14], the side effects of erythropoietin may not induce serious problems. This result is consistent with the outcome reported in other dysautonomic patients [14,15]. This evidence also supports that erythropoiesis and autonomic dysfunction may be strongly connected with each other.

Anemia is very frequent in FAP [1,17], but the reason had still not been elucidated. Sympathetic nerves innervate into the bone marrow and the kidney, which may influence on the erythropoiesis [19].

Precise investigation is needed to determine the mechanism of the development anemia and the effect of erythropoietin on anemia.

References