Revista Ciências da Saúde CEUMA RCS

ISSN 2965-6060

Relato de Caso

Resistance training and hematological responses: a case report with a patient with severe aplastic anemia

Treinamento de força e respostas hematológicas: relato de caso de um paciente com anemia aplástica grave

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Abstract

Aplastic anemia is a hematopoietic dysfunction that compromises pluripotent cells; the phenomenon that gives rise to the multiplication and maturation of the precursor or primordial cells of blood cells. It is commonly treated with immunosuppressive therapy and/or halogenic bone marrow transplantation. However, despite the comorbidities of aplastic anemia, studies associating physiological changes related to regular physical exercise are still scarce, possibly due to the low prevalence of the disease. Thus, we describe here the impact of a resistance training program on different hematological markers in a patient with severe aplastic anemia. A 39-year-old white male diagnosed with aplastic anemia 22 years ago underwent 12 weeks of resistance training. Different hematological markers were analyzed before and after 7 and 12 weeks of intervention. After the intervention an increase in reticulocytes and several other blood components were observed, the values of which remained within normal limits. In addition, there was a reduction in transaminases and liver enzymes that mark canalicular lesions, proving an improved liver condition. We conclude that after 12 weeks of strength training the patient presented positive changes in different hematological markers, such as erythrocytes, hemoglobin, hematocrit, neutrophils, and leukocytes, suggesting a positive effect of resistance training on the patient's clinical picture associated with the natural course of disease treatment.

Keywords: Aplastic anemia; Resistance training; Hematological markers.

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Renato André Sousa da Silva
E-mail: apicerenato@gmail.com
Fonte de financiamento:
Não se aplica
Parecer CEP
N. 166/2018-CONEP/SECNS/MS.
Procedência:
Não encomendado
Avaliação por pares:
Externa
Recebido em: 10/06/ 2023
Aprovado em: 30/07/ 2023

Como citar: Almeida DC, Rios WLO, Cruz CJG, Montecelli E, Sebastião E, Silva RAS. Resistance training and hematological responses: a case report with a patient with severe aplastic anemia. RCS Revista Ciências da Saúde - CEUMA, 2023;1(1):52-60. https://doi.org/10.61695/rcs.v1i1.4

Resumo

A anemia aplástica é uma disfunção hematopoiética que compromete células pluripotenciais; fenômeno que dá origem a multiplicação e maturação das células precursoras ou primordiais das células sanguíneas. É comumente tratada com terapia imunossupressora e/ou transplante de medula óssea halogênica. No entanto, apesar das comorbidades da anemia aplástica, ainda são escassos os estudos que associam alterações fisiológicas relacionadas à prática regular do exercício físico, possivelmente pela baixa prevalência da doença. Deste modo, descreve-se aqui os efeitos de um programa de treinamento resistido sobre diferentes marcadores hematológicos em um paciente com anemia aplástica grave. Um homem branco com 39 anos, diagnosticado com anemia aplástica há 22 anos foi submetido a 12 semanas de treinamento resistido. Diferentes marcadores hematológicos foram analisados antes e após 7 e 12 semanas de intervenção. Após a intervenção foi observado um aumento dos reticulócitos e de diversos outros componentes do sangue, cujo valores permaneceram dentro dos limites de normalidade. Adicionalmente, houve uma redução em transaminases e enzimas hepáticas marcadoras de lesões canalicular, indicando uma melhor condição hepática. Conclui-se que após 12 semanas de treinamento de força o paciente apresentou alterações positivas em diferentes marcadores hematológicos, como eritrócitos, hemoglobina, hematócrito, neutrófilos, e leucócitos, o que sugere um efeito positivo do treinamento resistido sobre o quadro clínico do paciente associadamente ao curso natural do tratamento da doença.

Palavras-chave: Anemia aplástica; Treinamento resistido; Marcadores hematólogicos.

INTRODUCTION

Aplastic anemia (AA) is a rare and potentially fatal disease of the hematologic stem cells because bone marrow is replaced by fat. About 70-80% of the cases of AA are idiopathic and occur by the destruction of the hematopoietic stem cells by an autoimmune phenomenon. Previous reports have demonstrated an incidence of AA of 2.35 cases per million inhabitants per year in Sweden (Vaht *et al.*, 2017), 300-600 cases annually in the United States (Savaşan *et al.*, 2018), and about 2.7 per million cases per year in Brazil (Hamerschlak, *et al.*, 2005). If untreated, AA may be associated with significant morbidity and mortality due to recurrent infections or bleeding. In fact, in Brazil, a recent study showed that between the years 2000 and 2018, there were over 35 thousand deaths related to AA (Santo *et al.*, 2022).

Common symptoms of AA include fatigue, shortness of breath, rapid or irregular heart rate, prolonged bleeding from cuts, and larger frequency of infections (Storb, 1997; Moore; Krishnan, 2019; Medinger *et al.*, 2018). Currently, treatment options for AA include blood transfusions, stem cell transplants, immunosuppressants, bone marrow stimulants, and antibiotics and antivirals (Scheinberg, 2011; Peslak *et al.* 2017; Robbins *et al.*, 2013).

Although the effect of aerobic training in patients with aplastic anemia is few reported in the literature, it is believed that exercise training may be an adjuvant treatment for individuals with AA as it can provide physical, mental, and physiological benefits for these patients. For instance, researchers demonstrated that an aerobic exercise program raised the hemoglobin levels of a non-severe AA carrier (Mangione *et al.*, 2000). On the other hand, no effects of resistance exercises for patients with AA have yet been reported in the literature. Resistance training has been highly recommended for individuals of all ages, even in the presence of a wide range of chronic diseases

and conditions. To this end, we aimed to report a successful case of a patient with severe AA that underwent a short resistance training program, and complained about fatigue, shortness of breath, and general weakness that limited his working capacity and negatively impacted his quality of life.

METHODS

This was an exploratory, descriptive case study, whose objective was to report the effects of a short-term resistance training program on hematological responses, of a white non-smoking male. Before the beginning of the study, the patient was informed about the possible risks and benefits of the intervention and signed the informed consent form in accordance with circular letter n. 166/2018-CONEP/SECNS/MS. The physical training program was conducted in a private fitness center from May to June 2021.

CASE REPORT

Subject

The subject was a white, Brazilian, non-smoking 39-year-old man (1.80 m, 92.5 kg). He is a self-employed professional with a college education. He signed the informed consent form before the beginning of the study, and his hematologist agreed to the physical stress tests/exercises. He was diagnosed with severe AA 22 years ago after medical attention prompted by his mother's observation that he was pale. He also reported fatigue, dyspnea, and general weakness that limited his ability to work. At the time, the subject also experienced frequent joint pain. The diagnosis of AA was confirmed by bone marrow biopsies and blood tests. The blood test values revealed that the disease was severe, with a large reduction in red blood cells, hemoglobin, and platelets.

Until the beginning of 2004, his treatment was based on CSA (cyclosporine) and corticoids (meticorten), at which time the possibility of transplantation was evaluated; however, the patient reacted well to the immunosuppressants. However, at the end of 2004, the disease worsened. It was then decided to add ATG (or GAT) serum therapy to the treatment. It was applied weekly and required subsequent isolation of the patient for recovery. In 2008, a second worsening of the disease required a new adjustment of drugs to stabilize the clinical picture. A combination of CSA, horse GAT, and corticoid was adopted. Between 2009 and 2011, the treatment returned to the use of only meticorten and cyclosporine. In 2012 shoulder surgery was performed to remove the abscess, which was aggravated by bacterial infection lodged in the head, forming 3 brain abscesses. For this

reason, another surgery was performed with ~ 90 days of hospitalization and the use of 4 or 5 different antibiotics to end 1 abscess that could not be removed. In 2014 the treatment was changed again by combining CSA and rabbit GAT and corticoid. Between 2013 and 2018 the treatment went through eventual and decreasing modulations of cyclosporine and corticoid dosages. During the data collection period regular treatment was maintained, and the clinical picture remained stable.

PROCEDURES

Laboratory Testing

The tests included disease markers (blood counts). Blood samples drawn from the antecubital vein were obtained: 24 h before the start of training (baseline), on the first day of the seventh week of training (W7), and 24 h after the last training of the twelfth week. The blood samples and the costs covered by the subject's health insurance plan were analyzed in an independent laboratory. Complete blood count, reticulocyte count, TGO, TGP, GAMA-GT, alkaline phosphatase, ferritin, transferrin saturation, iron, total cholesterol, triglycerides, glucose, glycated hemoglobin, urea, and creatinine were analyzed. The tests were performed by a private laboratory and the methods used for analysis were automated by fluorescence flow cytometry and impedance, with confirmation of counts and morphological analysis performed by microscopy, applicable; UV kinetic; colorimetric kinetic; immunoassay; electrochemiluminometric; enzyme assay. The reference values adopted were for males over 16 years old.

Resistance Training Protocol

The resistance training program lasted 12 weeks (W1-W12) and was conducted between November 2018 and January 2019 (Table 01). The frequency was three sessions per week, except for weeks S1 and S11 where only two training sessions occurred. The protocol involved the exercises of the anterior pull-up, straight supine, seated rowing on the pulley, machine development, extension chair, flexor table, standing plantar flexion on the machine, and trunk flexion on the machine. All exercises were performed in 3 sets between 8 and 10 maximum repetitions with 90 sec of passive rest. The loads (intensity) were continuously adjusted to reach concentric failure. During data collection, no other exercise routines were implemented.

Table 01 – Resistance Training Protocol

EXERCISES	LOADS											
	W1	W2	W3	W4	W5	W6	W7	W8	W9	W 10	W 11	W 12
Anterior pull-up	61	68	75	75	75	75	82	89	89	89	92	96
Straight supine	20	20	22,5	25	25	27,5	27,5	30	30	32,5	32,5	32,5
Seated rowing	61	65	70	75	75	75	80	85	85	85	90	90
Machine development	35	37,5	37,5	45	45	45	50	50	50	50	50	50
Extension chair	60	75	85	85	85	90	92,5	96	96	96	102	102
Flexor table	55	55	60	60	60	60	62,5	65	65	70	72,5	75
Standing plantar flexion	115	125	125	135	135	135	135	135	135	135	145	145
Trunk flexion	55	55	55	55	55	55	60	70	70	70	70	70

W (week) and 1 (one) = first week of resistance training (W1). Same as for the other abbreviations (W2-W12). Absolute loads expressed in kilograms (kg).

RESULTS

The findings suggest hematological changes related to the disease and resistance training. The analyzed markers varied in physiological levels or even demonstrated positive clinical changes associated with the resistance training program. Specifically in Table 2, there are changes such as increased erythrocytes, hemoglobin, and hematocrit.

Table 02 – Blood counts

Variable	Baseline	W7	W12	Δ1	Δ2	Δ3	RV
Erythrocytes	4,07	4,21	4,50	↑3.4	↑6.8	↑10.5	4,30 to 4,50 millions/mm^3
Hemoglobin	13,5	13,8	15,1	↑2.2	↑9.4	↑11.8	13,5 to 17,5 g/dL
Hematocrit	39	40,1	44	↑2.8	↑9.7	↑12.8	39 to 50 %
Corpuscular hemoglobin	33,2	32,8	33,6	↓1.2	↑2.4	↑1.2	26 to 34 pg
VCM	95,8	95,2	97,8	↓0.6	↑2.7	↑2.0	81 to 95 fL
Corpuscular hemoglobin	34,6	34,4	34,3	↓0.5	↓0.2	↓0.8	31 to 36 g/dL
RDW	12,3	12,8	12,9	↑4.0	↑0.7	↑4.8	11,8 to 15.6 %
Leukocytes	3.880	4.530	4.480	↑16.7	↓1.1	↑15.4	3.500 to 10.500/mm^3
Neutrophils	1.850	1.920	2.460	↑3.7	↑28.1	↑32.9	1.700 to 7.000/mm^3
Eosinophils	70	50	60	↓28.5	↑20	↓14.2	50 to 500/mm^3
Basophils	10	10	10	-	-	-	0 to 300/mm^3
Lymphocytes	1.390	1.870	1.370	↑34.5	↓26.7	↓1.4	900 to 2.900/mm^3
Monocytes	560	680	580	↑21.4	↓14.7	↑3.5	300 to 900/mm^3
Platelets	159.000	169.000	181.000	↑6.2	↑7.1	↑13.8	150.000 to 450.000/mm^3
Mean platelet volume	9.9	9.6	9.8	↓3.0	↑2.0	↓1.0	9.2 to 12.6 fL
Reticulocytes	100.900	101.000	103.500	↑0.09	↑2.4	↑2.5	30.000 to 100.000/mm^3
% Reticulocytes	2.4	2.4	2.3	-	↓4.1	↓4.1	-----
Iron	94	126	114	↑34.0	↓9.5	↑21.2	65 to 175 micro/dL
Reticulocyte fraction Immature (IRF)	13.4	7.4	11.1	↓44.7	↑50	↓17.1	2.1 to 14.9 %
Iron – Degree of Saturation	35	47	46	↑34.2	↓2.1	↑31.4	20 to 50%
Ferritin	272	389	441	↑43.0	↑13.3	↑62.1	26 to 446 micro/L

W7 = seventh week; W12 = twelfth week; Δ1 = difference (%) between the baseline condition and W7; Δ2 = difference (%) between condition W7 and W12; Δ3 = difference (%) between baseline condition and W12. Reference values (RV).

The results in Table 3 demonstrate discreet alterations in energy, lipids, and renal function.

Table 03 – Metabolic markers

Variable	Baseline	W7	W12	Δ1	Δ2	Δ3	RV
Glucose	106	96	109	↓9.4	↑13.5	↑2.8	75 to 99 mg/dL
Glycated hemoglobin	4.5	4.8	4.8	↑6.6	-	↑6.6	5,7 to 6,4 %
Total cholesterol	202	211	211	↑4.4	-	↑4.4	Until 190 mg/dL
Triglycerides	86	85	97	↓1.1	↑14.1	↑12.7	Fast 12 h < 150 mg/dL no fast of 12h 175 mg/dL
Urea	28	35	32	↑25	↓8.5	↑14.2	10 to 50 mg/dL
Creatinine	1.02	1.1	1.05	↑7.8	↓4.5	↑2.9	0.7 to 1.3 mg/dL

S7 = seventh week; S12 = twelfth week; Δ1 = difference (%) between baseline condition and S7; Δ2 = difference (%) between condition S7 and S12; Δ3 = difference (%) between baseline condition and S12. Reference values (RV).

As for the hepatological parameter, it is identified in Table 4 that there was a reduction in transaminases and liver enzyme markers of canalicular injury, indicating a better liver condition.

Table 04 – Liver markers

Variable	Baseline	W7	W12	Δ1	Δ2	Δ3	RV
AST (TGO)	40	49	35	↑22.5	↓28.5	↓12.5	Until 40 U/L
ALT (TGP)	78	77	71	↓1.2	↓7.7	↓8.9	Until 41 U/L
FAL	238	225	222	↓5.4	↓1.3	↓6.7	40 to 129 U/L
Gama-GT	514	538	560	↑4.6	↑8.9	↑4.0	12 to 73 U/L

W7 = seventh week; W12 = twelfth week; Δ1 = difference (%) between the baseline condition and W7; Δ2 = difference (%) between condition W7 and W12; Δ3 = difference (%) between baseline condition and W12. ALP: Alkaline Phosphatase. Reference values (RV).

DISCUSSION

This study aimed to report a case of a 39-year-old white non-smoking male patient with severe AA who undertook a resistance training program. The subject was able to successfully complete the program without any adverse health effects. Overall, the program showed promise in improving muscular strength performance and hematological parameters. More specifically, we observed an increase in erythrocytes, hemoglobin, hematocrit, leukocytes, and neutrophils after the intervention period. Collectively, these results suggest a positive effect of resistance training on different parameters of AA management, with clinical and functional relevance.

The findings observed after the intervention agrees with exercise-induced hematological effects previously reported in healthy individuals (Lippi; Sanchis-Gomar, 2019). It is well established that during exercise there is increased mechanical stress (muscle contraction, direct limb impact on the surface, and vasoconstriction) and metabolic stress (acidosis, shear stress, dehydration, and

oxidative stress) on the vascular system which results in increased hemolysis rate acutely (Lippi; Sanchis-Gomar, 2019). Thus, it is plausible to infer that the increase in reticulocytes observed in the present clinical case is a result of exercise-induced hemolysis, which possibly resulted in increased hematopoiesis (evidenced by increased erythrocytes, RBCs, hematocrit, WBCs, and neutrophils.

The increased erythrocyte and hemoglobin levels suggest increased O_2 and CO_2 transport capacity, which favors tissue oxygen delivery and maintenance of acid-base balance. These adaptations are clinical important since an imbalance in the partial pressure of these gases can result in reflex sympathetic hyperactivity and vagal depression, autonomic dysfunctions commonly associated with negative outcomes such as hypertension, myocardial infarction, and ventricular arrhythmias (Goldberger *et al.*, 2019). Furthermore, it is important to emphasize that despite the positive changes observed, even an absence of hematological effects after the intervention would already be a positive aspect giving of the possibility of increased neuromuscular performance without indications of worsening of the disease. In other words, the improvement in muscle function induced by resistance training without harming the treatment is already a great benefit and suggests that this type of exercise is a safe approach for this population, a hypothesis that needs to be confirmed in future longitudinal studies.

No changes were observed in blood glucose, glycated hemoglobin, and triglycerides after the intervention. However, it is important to note that these variables were within normal ranges even before the intervention. Thus, given that strength training promotes clinically relevant adaptations in the glycemic profile of hyperglycemic patients (Evans *et al.*, 2019), this adaptation may be more evident in conditions where glycemic homeostasis is compromised.

There is abundant evidence showing beneficial changes in the levels and chemical composition of the fractions and subfractions of HDL-cholesterol and LDL-cholesterol after an exercise program of different intensities, durations, and frequencies, performed by individuals of various age groups and fitness levels. Since we did not measure the fractions (HDL and LDL), we cannot say that this totality of cholesterol is harmful to the life of the patient, since we do not know which fraction is more altered.

In AA, erythropoiesis is ineffective with a reduction in the half-life of red blood cells. This deficit is maintained even during physical exercise, where under normal conditions, the tissue's need for oxygen would stimulate erythropoiesis (Weaver; Rajaram, 1992). During moderate exercise, there is an increase in intraerythrocyte 2,3-diphosphoglycerate, which shifts the hemoglobin dissociation curve to the right, providing more oxygen to the tissues, including the kidneys, where

there is a preference to synthesize erythropoietin. Consequently, the stimulus on the bone marrow is reduced, slowing down erythropoiesis in this tissue (Parr; Bachman; Moss, 1984).

Finally, it is important to note that, before to the intervention, the patient had high levels of TGO, TGP, FAL, and Gamma-GT, a characteristic suggestive of liver dysfunction. In this sense, except for Gamma-GT, all markers were reduced (although still above reference values). Thus, the practice of resistance training associated with conventional treatment was accompanied by positive changes in liver markers, which reinforces the hypothesis that patients with AA may benefit from this model of intervention. Because AA patients suffer from multiple transfusions. The results of this case report suggest that strength training may be associated with a decrease in the number of transfusions and liver iron overload, improving quality of life and willingness to perform daily activities.

The nature of the study is a limitation, which does not allow any relation of cause and effect. However, the findings of the present report are relevant in the face of the rare nature of the clinical picture in question and contribute in an important way to the scientific advance on the possible hematological impact of physical exercise in patients with AA.

CONCLUSION

The present case report demonstrates a healthy increase in cellular blood components in a patient with severe aplastic anemia associated with 12 weeks of resistance training.

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