Research Article

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Nerve excitability in iron deficiency anemia: a prospective study

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Abstract

Objective: The aim of this study was to evaluate the effects of iron deficiency anemia (IDA) on peripheral nervous system via nerve excitability tests (threshold tracking).

Methods: The study was performed on 32 patients (22 patients (69%) with moderate, and 10 patients (31%) with severe IDA. Parenteral iron treatment was administered based on the calculated iron deficiency. Three nerve excitability tests were performed; Test 1: During the pre-treatment period, Test 2: On the 7th day of the post-treatment period, and Test 3: Three months after the correction of anemia. The strength-duration/time constant (tSD), rheobase and supernormality values of motor and sensory axons of the median nerve were recorded.

Results: A statistically significant stepwise increase in the supernormality periods of the sensory axons of the median nerve was detected between the tests conducted in three separate times ($p<0.01$). This increase significantly correlated with hemoglobin levels but not with iron levels. However, there was no significant difference in tSD and rheobase values between the tests on both motor and sensory axons. A significant correlation observed between the increase of sensorial supernormality and hemoglobin levels.

Conclusion: The significant increase of supernormality in sensory axons of the peripheral nerves may suggest that chronic ischemia occurring in IDA may have some impacts on fast acting K channels. The causes of the decrease in supernormality of sensory axons can make contribution to the pathogenesis of the patients' complaints, such as abnormal sensation and dysesthesia in their extremities.

Keywords: Nerve excitability, anemia, iron deficiency, threshold tracking

INTRODUCTION

The symptoms of iron deficiency anemia (IDA) are generally regarded as nonspecific and sometimes resulting from altered tissue oxygenation (1-8). Whether the origin of some of the symptoms is central or peripheral is unknown (8, 9). The results of routine nerve conduction studies are usually inconclusive in IDA (8-10). Threshold tracking techniques enable us to understand the changes in the membrane properties by means of the different indices of axonal excitability that can not be demonstrated by routine electrodiagnostic studies (11-16).

In the last decade, these tests have been used increasingly and contributed to our understanding of the pathophysiology of various diseases (17-26). Peripheral nerve node, paranode and internodal conditions can be studied in vivo in human subjects by nerve excitability tests like rheobase, supernormality, refractoriness, strength-duration time constant (tSD), threshold electrotonus, and latent addition. These tests allow us to make predictions about the influences of diseases on ion channels (11-26). In this study, it is hypothesized that iron deficiency and/or IDA cause the changes in the ion channel functions and accordingly in the peripheral nerve axonal excitability and iron treatment restore this functions. Our aim is to find whether iron deficiency and/or IDA cause major changes in the ion channel functions and whether these functions can be restored by both axonal excitability in the peripheral nerve and iron treatment. To our knowledge, this is the first study that examines the changes in peripheral nerve excitability in IDA.

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METHODS

Patients

Tests were performed on 32 patients; with 30 women (93.8%) and 2 men (6.2%). Among the patients, 22 of them (69%) had moderate and 10 of them (31%) had severe IDA with varying etiologies. The patients who were admitted to the Hematology Department for a year were guided to the electromyography (EMG) laboratory for the nerve conduction studies. Patients were otherwise healthy and none of them were suffering from a peripheral nerve disorder or a disease process that could affect peripheral nerve function. Ethics committee approval was received for this study from the ethics committee of Abant İzzet Baysal University School of Medicine (Decision No: 2006/100-66). Written informed consent was obtained from patients.

All patients received parenteral iron treatment with iron sucrose (Venofer®, 500 mg a day for 5 hours, every 100 mg drug was diluted within 100 ml of 0.9% NaCl) following the calculation of iron deficiency for each patient (total dose (mg)=-weight (kg) x (normal hemoglobin value (gr/dL) – patient's hemoglobin value) x 2.4 + 500 mg) (27). Patients' whole blood samples were collected to perform the complete blood count, blood iron level, total iron binding capacity, transferrin saturation rate and reticulocyte number, and peripheral smear was examined before the iron treatment, seven days after treatment, and also after the correction of IDA (in the third month). Additionally, the electrophysiologic examinations were performed for three times; the first one-labeled as Test 1 was performed before the treatment while the second one –Test 2-and the third one –Test 3-were performed 7 days after the treatment and 3 months after the treatment respectively.

Electrophysiologic Examination

The experiment was performed with an EMG device (Viking IV, Nicolet Biomedicals, Madison, USA). Recordings were made with standard surface electrodes made from Ag-AgCl (10 mm diameter, Nihon Kohden, NM-312S). Patients were recorded from 08.00 am to 07.00 pm. The subjects were laid down in a comfortable supine position in a quiet, well lit air conditioned room maintained at 24±1°C. The skin temperature of each subject was over 32°C (skin temperature was monitored continuously and was kept above 32°C). The arm without catheter was preferred for examination. Before threshold tracking measurements, the tibial and median nerve motor NCVs and F waves, sural and median nerve sensory NCVs were examined in each subject.

In threshold tracking measurements, the electrical stimuli were applied over the median nerve at the wrist. For motor axons, the compound muscle action potentials (CMAPs) was recorded from abductor pollicis brevis muscle and for the sensory axons, the compound sensory action potential (CSAP) of cutaneous afferents in the median nerve was recorded antidromically from the index finger, using the technique of threshold tracking, as described by Kiernan et al. and Weigl et al. (28, 29). Stimuli were delivered at every 1 second. First, a supramaximal stimulus was delivered to produce a maximal CMAP or CSAP. Then, the intensity of the test stimulus was adjusted to keep the test CMAP or CSAP at 40% of maximum. The current required to produce a CMAP and a CSAP with the amplitude 40% of maximum is referred to as the 'threshold' for the CMAP and CSAP. The strength–duration time constant (tSD) was determined from the thresholds obtained with unconditioned test stimuli of 0.1 and 1.0 ms duration (*I*0.1 and *I*1.0, respectively), in accordance with Weiss' Formula (tSD and rheobase measurements was calculated according to the following formula : tSD (ms) = 0.1 x (I 0.1 - I 1.0) / (I 1.0- 0.1 x I 0.1) Rheobase (mA) = (I 1.0- 0.1x I 0.1) / 0.9)) (14, 30-32). 'Supernormality' for a CSAP and CMAP was measured as the percentage reduction in threshold when the test stimulus was preceded by supramaximally conditioning stimulus, using a conditioning-test interval of 8 ms and 10 ms respectively.

Although these tests generally are conducted with computerized threshold tracking program (QTRAC, Institute of Neurology, Queen Square, London, UK), we tried to make all measurements manually with four channel EMG-EP machine (Nicolet Viking). The conditioned potential was measured after subtraction of the response evoked by the conditioning stimulus alone.

Statistical Analysis

First, the Kolmogorov-Smirnov test was used to assess the normality of the data. Repeated measures ANOVA was used for within-subject comparisons; and based on the results, simple contrast and Bonferroni tests were conducted. Pearson correlation coefficient was used to check the relationship between the hemoglobin, iron, total iron binding capacity, and ferritin levels. In pairwise comparison between same motor and sensory excitability parameters for each time period, paired student t test was used. Statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS Inc.; Chicago, IL, USA).

RESULTS

Experiments were performed on 32 patients (30 women, 2 men). The mean age for the patients was 33.87±9.76 years (age range 18-52 years). Nerve conduction studies and F waves were all in normal range in each subject. The mean level of hemoglobin, iron, TIBC and transferrin saturation during three tests are shown in Table 1. Hemoglobin level showed a statistically significant increase in Test 2 and 3 when compared with the basal level obtained in Test 1 ($p<0.001$ for all). Iron level increased significantly in Test 2 when compared with Test 1 ($p<0.001$). TIBC did not differ significantly between Test 1 and 2, however in Test 3, TIBC showed a significant decrease when compared both with Test 1 and Test 2 ($p<0.001$). Transferrin saturation significantly increased in Test 2 and 3 when compared with

Table 1. The means and significance levels* of the hemoglobin, iron, total iron binding capacity (TIBC) and transferrin saturation values for three testing periods

	Test 1	Test 2	Test 3	p*
Hemoglobin (gr/dL)	7.4±1.15	8.7±0.94	12.7±0.71	0.001
	Test 2-1 / Test 3-2 / Test 3-1p=0.001			
Iron (µg/dL)	8.3±3.	58.6±23.2	67.1±26.1	0.01
	Test 2-1 / Test 3-1 p=0.001; Test 3-2 p=0.46			
TIBC (mg/dL)	363±21.9	347±47.8	322±44.3	0.01
	Test 2-1 p=0.2; Test 3-2 p=0.001; Test 3-1 p=0.01			
Transferrin saturation (%)	2.29±0.86	16.87±5.81	20.77±7.99	0.01
	Test 2-1 / Test 3-1 p=0.001; Test 3-2 p=0.065			

*Significance level p<0.05 (Repeated Measures Analyses, Bonferroni test)
All values were given as means ± standart deviations

Table 2. The means and significance levels* of the rheobase, strength-duration/time constant (tSD) and supernormality values of the motor and sensory axons for three testing periods

	Test 1	Test 2	Test 3	p*
Motor axons				
Rheobase (mA)	3.84±1.86	3.51±1.36	3.64±1.34	0.586
tSD (ms)	0.25±0.05	0.25±0.10	0.25±0.03	1.000
Supernormality (%)	12.6±4.8	12.28±3.61	12.81±3.51	0.653
Sensory axons				
Rheobase (mA)	2.89±1.41	2.72±1.05	3.02±1.39	0.516
tSD (ms)	0.29±0.06	0.31±0.07	0.29±0.06	0.243
Supernormality (%)	9.25±4.21	11.75±3.99	14.46±4.36	0.001
		Test 2-1 p=0.01; Test 3-2 / Test 3-1 p=0.001		

*Significance level p<0.05 (Repeated Measures Analyses, Bonferroni test)
All values were given as means ± standart deviations

Test 1 (p<0.001). The mean values of motor and sensory rheobase, tSD and supernormality are shown in Figure 1, Figure 2 and Figure 3 respectively. There was no significant difference in sensory rheobase between tests, and the motor rheobase did not show significant difference after iron treatment and also after the correction of anemia when compared with Test 1 (Table 2). Sensory rheobase was significantly lower than motor rheobase in Test 1 and in Test 2 (independent student-t test; p: 0,012), however, this significant difference has disappeared in Test 3 although the mean of the sensory rheobase was still lesser than the mean of the motor rheobase. There was no significant difference both in motor and sensory tSD between tests respectively). Sensory tSD was significantly higher than motor tSD for all of the three tests (independent student-t test, p=0.033, p=0.012, p=0.002 respectively). There was a statistically significant difference between the groups in the mean sensory supernormality values (repeated measures, p<0.01, Table 2). However, we could not find any significant difference in the other parameters tested. The calculated supernormality values in Test 2 and 3 were significantly higher than Test 1.

Sensory supernormality level showed the highest increase in Test 3 while the hemoglobin level reached the most pronounced increase. There was a positive correlation between the sensory supernormality values and the hemoglobin levels (Pearson correlation efficient**;** 0.499, p<0.001). When we

Figure 1. The mean rheobase values of motor and sensory axons

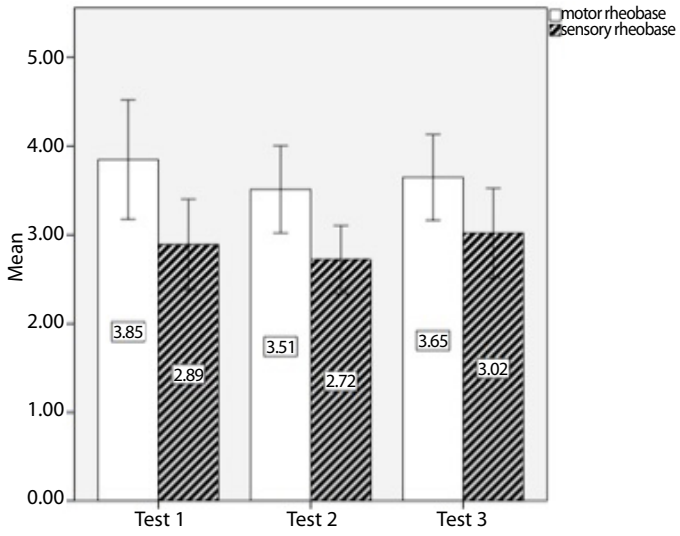
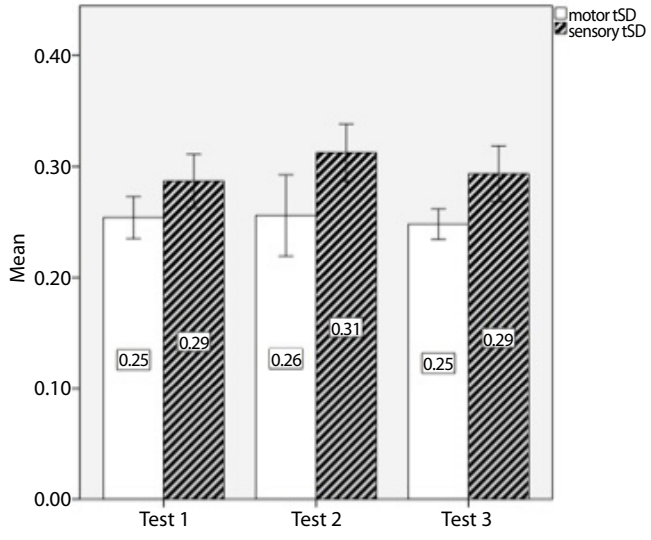


Figure 2. The mean strength-duration/time constant (tSD) values of motor and sensory axons

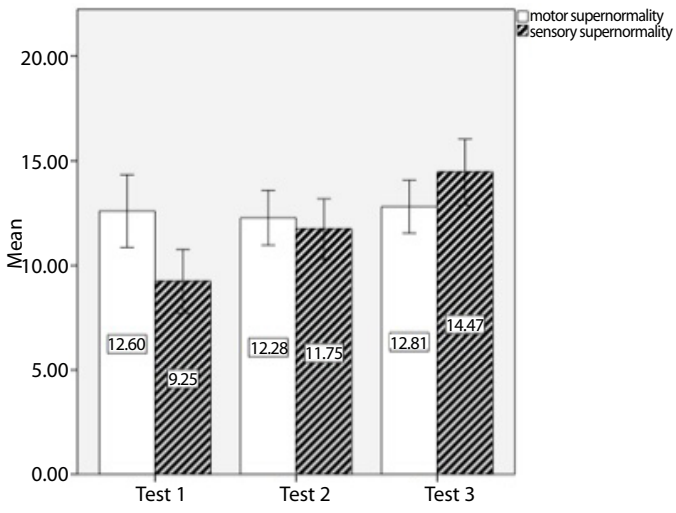


grouped the subjects according to the basal hemoglobin levels, 22 patients (68.8%) had moderate and 10 patients (31.3%) had severe anemia. However, the difference was not significant in sensory supernormality values between patients with moderate or severe anemia (10.1±4.43 and 7.4±3.13 respectively, independent student-t test, $p>0.05$). Correlation efficient values were weak for iron and total iron binding capacity (0.350, $p<0001$; -0.220, $p<0.005$).

DISCUSSION

In this study, we observed no significant difference in nerve conduction studies and F waves between Test 1, 2 and 3. Also, there was no significant difference in tSD and rheobase values of motor and sensory axons between repeated tests. Sensory supernormality values showed a significant stepwise increase, lowest in Test 1 and highest in Test 3, however, supernormality of motor axons did not show a similar significant increase. Furthermore, there was a positive correlation between sensory supernormality values and hemoglobin levels.

Figure 3. The mean supernormality values of motor and sensory axons



The routine electroneuromyographical (ENMG) examination is expected to be unremarkable in IDA (8-10). In a case report by Arturo Leis et al., a patient with severe anemia showed some anomalies in H reflex and F wave responses which improved after blood transfusion (33). However, current study could not detect any abnormality in routine ENMG examination and any significant change after the improvement of IDA.

Human cutaneous afferents have a longer tSD and lower rheobase than α motor axons (16, 26). The greater expression of a very slowly inactivating (persistent) Na conductance is thought to be responsible for these properties (34). In addition, threshold channels which were more densely expressed on sensory axons, extracelluler H+, Ca2+ ions and changes in pCO_2 can play a role in this feature (25, 34-38). In this study, sensory axons showed longer tSD and lower rheobase than motor axons in all three tests, which is compatible with the conclusions in the literature.

Both rheobase and tSD of motor and sensory axons were not significantly different between Test 1, 2 and 3 in this study. These two indices of axon excitability are affected by the features of nodal membranes. Theoretically, tSD gives indirect information about the non-voltage dependent persistant Na channels (24-26). In studies performed after acute ischemia, it was found that rheobase decreased and tSD increased both on motor and sensory axons (25, 39). Some of the complaints observed in IDA may be arising from ischemia. However this study did not detect any change in rheobase and SDTC values. Chronic ischemia with adaptation could be an explanation for this invariance as IDA would cause chronic ischemia rather than acute ischemia.

Supernormal period is a period which needs lower stimulus intensity for the threshold. This period substantially depends on paranodal fast K channels (28, 40). Sensory axons show lower supernormality than motor axons (40). In Test 1, sensory supernormality values were significantly lower than motor supernormality values ($p<0.05$). Following treatment with iron, in Test 2 and 3, this difference was lost. It was observed that sensory supernormality increased in a stepwise fashion between tests; lowest in Test 1, higher in Test 2 and the highest in Test 3. This increase was statistically significant compared both with the first or previous one ($p<0.05$ and $p<0.001$). In Tests 2 and 3, there was no marked correlation between sensory supernormality increase and iron level or total iron binding capacity level, however this increase was correlated with hemoglobin level. This finding led us consider that the correction of the chronic ischemia may be responsible for this increase in supernormality of sensory axons rather than iron itself. To derive more clear conclusions about the influence of iron on sensory supernormality, a future study may be done with patients with iron deficiency without anemia. Chronic ischemia like the acute one may cause inactivation in fast K channels and could be a possible cause for the decrease in sensory supernormality in Test 1 (24, 25, 41). On the other hand, approaching and even exceeding supernormality values of the sensory axons in comparison with the values of the motor axons after treatment, recalls excessive activation of the fast K channels. Supernormality of motor axons did not show a similar change like sensory axons between the tests. Motor axons may be more resistant than the sensory axons to chronic ischemia or may show a better adaptation than the sensory axons. The reasons that cause the changes in supernormality of sensory axons may explain the complaints of abnormal sensations and dysesthesia occurring on extremities of IDA patients.

The important limitation of the present study is the lack of the healthy control group with the same age interval. If we could have included it, we could have said IDA whether caused axonal excitability abnormalities from the beginning and we could be more precise about iron treatment effects. So, there is a need a new complementary study comparing the IDA patients with the healthy individuals.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Abant İzzet Baysal University School of Medicine (2006/100-66).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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