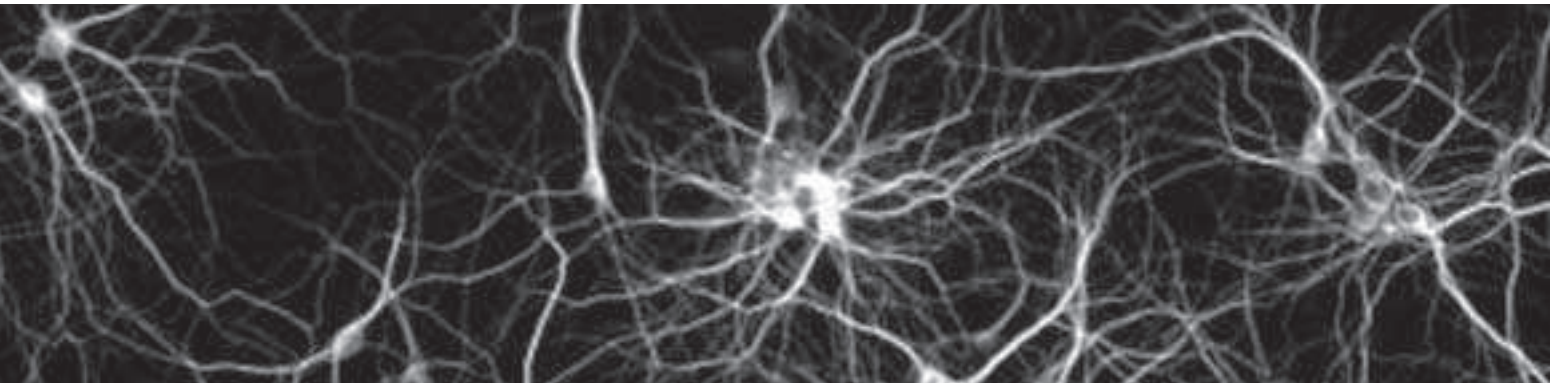

Electrophysiological changes in iron deficiency anemia

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ABSTRACT - Iron deficiency anemia (IDA) is the most common nutritional problem worldwide. Owing to the role of iron in brain energy metabolism, neurotransmitter function and myelin formation, IDA may lead to behavioral, developmental and cognitive dysfunctions. Iron is an essential element and has an important role in several metabolic and enzymatic processes including NADPH reductase activity and cytochrome oxidase system. Our aim was to investigate the electrophysiological effects of IDA on the peripheral nervous system, and to evaluate whether or not the possible electrophysiological abnormalities are reversible with appropriate doses of iron therapy. Electrophysiological evaluations were performed in 52 patients with newly diagnosed IDA and 30 age-matched healthy controls. Electrophysiological evaluations were repeated after 3 months of oral iron therapy. Normal electrophysiological findings were recorded in 38 (73.07%) patients, while 4 (7.69%) patients had polyneuropathy (PNP) and 10 (19.24%) had carpal tunnel syndrome (CTS) findings. Except for one patient with PNP and CTS findings each, the electrophysiological findings of all patients were found to have returned to normal ranges after 3 months of oral iron therapy. Detection of iron responsive neuropathic processes (PNP and CTS) in IDA patients suggested that IDA may cause peripheral nervous system involvement. It is important to emphasize the examinations for IDA as an etiologic factor on planning treatment for neuropathy patients. In cases where IDA is present, it would be beneficial to treat IDA with iron before applying other treatment options for neuropathy.

Key words: carpal tunnel syndrome, electrophysiological evaluations, iron deficiency anemia, oral iron replacement, polyneuropathy

INTRODUCTION

Anemia is a common morbidity, which can be defined as a decline in red blood cell (RBC) mass or in serum hemoglobin concentrations according to

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the reported normal age and sex based values (1). Using the World Health Organization definition of anemia (hemoglobin level less than 13 g/dL (130 g/L) in men and less than 12 g/dL (120 g/L) in women), more than 10 percent of persons older than 65 are anemic. The prevalence increases with age, approaching 50 percent in chronically ill patients living in nursing homes (2,3).

It can be asymptomatic, or can present in a variety of symptoms, especially when serum Hb values decrease to 8-9.5 g/dL. Whether symptomatic or not, it is reported that an appropriate therapy may prevent long-term complications of anemia (4).

Iron deficiency anemia (IDA) is known as the most common nutritional deficiency anemia worldwide, affecting approximately 30% of the general population (5). While it is a hypochromic and microcytic anemia, microcytosis and hypochromia are defined as a decline in the serum mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) values according to the reported age and sex related normal values of these parameters (1,6). The diagnosis of IDA can be made by detecting serum iron and ferritin levels below normal ranges with an increase in the serum total iron binding capacity (TIBC) values, in addition to laboratory established hypochromic microcytic anemia (5,7).

While iron is an essential element that plays an important role in neurotransmitter metabolism, cerebral energy metabolism, and myelin formation, IDA can cause dysfunctions of the central nervous system such as decline and slowing of cognitive functions, delayed growth and motor development, especially in childhood, and learning and memory disorders. IDA can also cause dysfunctions in the peripheral nervous system, such as paresthetic complaints due to generalized neuropathic processes caused by the effect of iron on myelin formation (6,8-10).

The aim of this study was to investigate electrophysiologically the interaction of IDA with the peripheral nervous system, and to investigate whether or not the possible electrophysiological abnormalities are reversible with the appropriate doses and duration of iron therapy.

MATERIALS AND METHODS

Consecutive patients aged over 20 with the diagnosis of IDA were recruited from the outpatient clinics of our university hospital. They were newly diagnosed and had not received any medical treatment for anemia or its complications. Before enrolment, the purpose and procedures of the study were fully explained to each individual and written consent was obtained from them. Initially, to confirm anemic status and eliminate other possible causes of peripheral nervous system (PNS) disorders, complete blood count, vitamin B12 and folic acid tests, thyroid function tests (free T3, free T4 and TSH) and routine biochemical serum tests were performed in each patient. Based on these analyses, patients with Hb levels strictly less than 11 g/dL and hematocrit (Htc) levels strictly less than 35% were considered anemic. IDA was diagnosed based on the presence of microcytosis (MCV <80 fl; MCH <27 pg; and MCHC <31 g/dL) and depleted iron stores (serum iron level <30 g/dL; serum ferritin level <15 g/dL; TIBC >360 μg/dL; and red cell division width (RDW) >14.8%) (7).

Exclusion criteria were as follows: patient age <20; history of mental, systemic, cardiac, renal, hepatic, endocrine, peripheral nervous system or infectious disease; nutritional deficiency; family history of peripheral nerve disease; drug and/or alcohol addiction (alcohol consumption more than 15 units/week); uncooperative patients; patients having taken any drug for any reason in the previous four weeks; and IDA patients on iron treatment.

All patients in the study group with a confirmed diagnosis of IDA underwent electrophysiological evaluation. The electrodiagnostic studies were performed with a MytoII EBNeuro device and according to standard techniques (11), at least on both arms and one leg. Motor nerve conduction studies included determination of conduction velocity, amplitudes and latencies after stimulation of the median, ulnar, peroneal and tibial nerves. Sensory nerve conduction studies included antidromic determination of conduction velocity, latencies and amplitude of the sensory nerve action potential of the median, ulnar, radial and sural nerves. The F responses of the median and peroneal nerves were also studied. Carpal tunnel syndrome (CTS) was diagnosed when the median nerve distal motor and/or sensory latencies exceeded 4.4 and 3.5 ms, respectively (12). The distance between stimulation site and active electrode was 14 cm for the median nerve sensory study. Polyneuropathy (PNP) was classified as axonal when the amplitude of either or both of the motor and sensory action potentials was decreased, but conduction times (velocities, distal latencies, and F-wave latencies) remained normal. Polyneuropathy was classified as

demyelinating when a significant increase of conduction times (velocities, distal latencies, and F-wave latencies) contrasted with a relative preservation of distal amplitudes (13).

Following these baseline electrophysiological evaluations, all patients were treated with 570 mg of oral ferroglycine sulfate, once daily. After 3 months of oral iron therapy, all patients whose red blood cell and biochemical values had reached normal range according to our reference laboratory values underwent final electrophysiological evaluation.

Statistical analyses were performed by Student's t-test on SPSS 10.0 database. All values were expressed as mean ± SD and $P<0.05$ values were considered statistically significant.

RESULTS

Fifty-two patients including five (9.7%) men and 47 (90.3%) women with newly diagnosed IDA, mean age 32.96±9.55 (range, 20-60) years, were enrolled in the study. Control group consisted of 30 healthy individuals including 22 (73.33%) women and eight (26.67%) men, mean age 33.66±8.78 (range, 22-60) years, similar to the study group ($P<0.05$).

The mean values of complete blood count and biochemical anemia parameters in IDA patients before and after iron replacement therapy are shown in Table 1. All anemia parameters seemed to have returned to normal values after 3 months of oral iron treatment and this recovery was statistically significant ($P<0.05$).

Comparison between the initial electrophysiological evaluation values in the IDA group and electrophysiological evaluation in the control group is shown in Table 2. Bilateral median nerve motor and sensory nerve conduction values, unilateral radial nerve conduction velocities, and peroneal nerve motor distal latency, tibial nerve motor conduction values (distal latency, amplitude, and nerve conduction velocity) with sural sensory nerve conductions, were statistically significant when compared with the control group ($P<0.05$). Prolonged peroneal nerve distal latencies were found and right median nerve and sural nerve sensory conduction velocities were slower than the reported normal reference values (11).

The electrophysiological values of IDA patients before and 3 months after oral iron treatment are summarized in Table 3. After 3 months of oral iron treatment, we found a statistically significant recovery in the motor (median nerve distal latency and ulnar nerve CMAP amplitudes bilaterally, and tibial nerve conduction velocities) and sensory nerve conduction studies (median nerve SNAP amplitudes and nerve conduction velocities bilaterally, and radial nerve SNAP amplitudes and nerve conduction velocities) in the patients when compared with the pretreatment electrophysiological values ($P<0.05$).

Table 1. *Mean values of complete blood count and biochemical anemia parameters in iron deficiency anemia patients before and after iron replacement therapy*

Anemia parameters	Before treatment	After treatment	t value	*P* value
Hb (g/dL)	9.81±0.42	12.94±0.48	-40.816	0.00
Htc (%)	28.79±1.56	41.89±2.06	-39.904	0.00
MCV (fl)	74.17±2.56	86.18±2.47	-25.012	0.00
MCH (pg)	24.87±0.91	29.01±0.82	-24.071	0.00
MCHC (g/dL)	28.01±1.79	33.93±0.85	-20.931	0.00
Iron (μg/dL)	24.23±4.92	65.98±10.55	-24.777	0.00
Ferritin (μg/dL)	12.26±0.97	46.13±11.08	-22.023	0.00
TIBC (μg/dL)	560.05±47.50	322.28±55.70	22.566	0.00
RDW (%)	17.73±1.83	12.41±0.55	20.632	0.00

P<0.05 = statistically significant; Hb = hemoglobin; Htc = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; TIBC = total iron binding capacity; RDW = red cell distribution width

Table 2. *Electrophysiological evaluation values in iron deficiency anemia (IDA) patients before treatment in comparison with control group*

	IDA group before treatment (n=52)	Control group (n=30)	t value	*P* value
MOTOR				
Left median				
Distal latency (ms)	3.08 ± 0.71	2.62 ± 0.36	3.280	0.002
Amplitüde (mV)	14.02 ± 4.49	18.16 ± 3.57	-4.318	0.000
NCV (m/s)	55.84 ± 3.96	57.80 ± 3.59	-2.224	0.029
Right median				
Distal latency (ms)	3.29 ± 0.94	2.43 ± 0.36	4.771	0.000
Amplitude (mV)	15.92 ± 5.29	18.17 ± 3.69	-2.047	0.044
NCV (m/s)	53.65 ± 4.56	56.38 ± 4.19	-2.687	0.009
Left ulnar				
Distal latency (ms)	2.27 ± 0.29	2.34 ± 0.24	-1.096	0.276
Amplitude (mV)	12.45 ± 4.31	21.58 ± 6.35	-7.727	0.000
NCV(m/s)	59.82 ± 5.63	58.32 ± 3.87	1.298	0.198
Right ulnar				
Distal latency (ms)	2.39 ± 0.49	2.31 ± 0.25	0.817	0.417
Amplitude (mV)	12.54 ± 4.12	19.92 ± 5.32	-6.998	0.000
NCV (m/s)	57.00 ± 6.51	58.20 ± 4.04	-0.906	0.367
Peroneal				
Distal latency (ms)	4.72 ± 1.09	4.31 ± 0.26	1.997	0.049
Amplitude (mV)	8.20 ± 3.03	8.58 ± 1.31	-0.649	0.518
NCV (m/s)	47.20 ± 4.63	48.40 ± 2.36	-1.318	0.191
Tibial				
Distal latency (ms)	3.91 ± 0.88	4.59 ± 0.32	-4.005	0.000
Amplitude (mV)	13.48 ± 5.42	8.65 ± 2.91	4.509	0.000
NCV (m/s)	42.72 ± 4.55	46.68 ± 2.43	-4.392	0.000
SENSORY				
Left median				
Distal latency (ms)	2.53 ± 1.13	2.56 ± 0.35	-0.172	0.864
Amplitude (μV)	42.84±25.37	25.89 ± 3.77	3.627	0.001
NCV (m/s)	52.54 ± 6.92	57.05 ± 4.02	-3.255	0.002
Right median				
Distal latency (ms)	2.71 ± 1.28	2.45 ± 0.33	1.084	0.282
Amplitude (μV)	36.24 ± 21.62	23.84 ± 4.92	3.087	0.003
NCV(m/s)	51.20 ± 10.43	56.50 ± 4.20	-2.657	0.010
Left ulnar				
Distal latency (ms)	2.05 ± 0.64	2.30 ± 0.31	-2.014	0.047
Amplitude (μV)	35.73 ± 20.13	25.83 ± 4.82	2.643	0.010
NCV (m/s)	53.15 ± 5.64	58.15 ± 4.19	-4.225	0.000
Right ulnar				
Distal latency (ms)	2.01±0.50	2.27 ± 0.30	-2.603	0.011
Amplitude (μV)	45.33 ± 19.64	24.49 ± 4.51	5.712	0.000
NCV (m/s)	55.80 ± 4.60	58.41 ± 4.21	-2.550	0.013
Radial				
Distal latency (ms)	2.27 ± 0.84	2.52 ± 0.14	-1.626	0.108
Amplitude (μV)	16.26 ± 10.27	20.19 ± 3.48	-2.025	0.046
NCV (m/s)	51.75 ± 7.41	57.32 ± 3.68	-3.849	0.000
Sural				
Distal latency (ms)	2.90 ± 1.01	3.97 ± 0.51	-5.353	0.000
Amplitude (μV)	21.16 ± 22.41	8.09 ± 1.74	3.178	0.002
NCV (m/s)	42.48 ± 14.19	48.17 ± 2.15	-2.175	0.033
F wave				
Median				
Distal latency (ms)	23.20 ± 11.53	24.82 ± 2.14	-0.759	0.450
Peroneal				
Distal latency (ms)	43.80 ± 10.40	43.53 ± 3.85	0.138	0.890

NCV = nerve conduction velocity; ms = millisecond; uV = microvolt; m/s = meter/second; P<0.05 = statistically significant

Table 3. *Electrophysiological values in iron deficiency anemia (IDA) patients before and after treatment*

	Before treatment IDA group (n=52)	After treatment IDA group (n=52)	T value	*P* value
MOTOR				
Left median	3.08 ± 0.71	2.72 ± 0.49	2.993	0.003
Distal latency (ms)	14.02 ± 4.49	14.25 ± 4.25	-0.267	0.790
Amplitude (mV)	55.84 ± 3.96	56.16 ± 4.18	-0.399	0.691
NCV (m/s)	3.29 ± 0.94	2.96 ± 0.48	2.271	0.025
Right median	15.92 ± 5.29	17.17 ± 4.69	-1.271	0.207
Distal latency (ms)	53.65 ± 4.56	54.77 ± 3.05	-1.480	0.142
Amplitude (mV)				
NCV (m/s)				
Left ulnar				
Distal latency (ms)	2.27 ± 0.29	2.43 ± 0.86	-1.262	0.210
Amplitude (mV)	12.45 ± 4.31	14.75 ± 4.55	-2.643	0.010
NCV (m/s)	59.82 ± 5.63	58.99 ± 5.15	0.790	0.432
Right ulnar	2.39 ± 0.49	2.30 ± 0.25	1.200	0.233
Distal latency (ms)	12.54 ± 4.12	14.44 ± 5.33	-2.031	0.045
Amplitude (mV)	57.00 ± 6.51	58.92 ± 4.92	-1.696	0.093
NCV (m/s)				
Peroneal				
Distal latency (ms)	4.72 ± 1.09	4.43 ± 1.00	1.379	0.171
Amplitude (mV)	8.20 ± 3.03	8.93 ± 3.49	-1.132	0.260
NCV (m/s)	47.20 ± 4.63	48.78 ± 5.00	-1.668	0.098
Tibial				
Distal latency (ms)	3.91 ± 0.88	3.92 ± 0.86	-0.045	0.964
Amplitude (mV)	13.48 ± 5.42	14.29 ± 5.46	-0.758	0.450
NCV (m/s)	42.72 ± 4.55	46.40 ± 3.77	-4.484	0.000
SENSORY				
Left median	2.53 ± 1.13	2.35 ± 0.65	0.963	0.338
Distal latency (ms)	42.84 ± 25.37	54.02 ± 23.07	-2.350	0.021
Amplitüde (μV)	52.54 ± 6.92	55.42 ± 6.24	-2.229	0.028
NCV (m/s)	2.71 ± 1.28	2.35 ± 0.54	1.834	0.070
Right median	36.24 ± 21.62	52.62 ± 19.50	-4.056	0.000
Distal latency (ms)	51.20 ± 10.43	54.90 ± 5.35	-2.278	0.025
Amplitude (μV)				
NCV (m/s)				
Left ulnar				
Distal latency (ms)	2.05 ± 0.64	2.02 ± 0.45	0.229	0.819
Amplitude (μV)	35.73 ± 20.13	38.85 ± 19.12	-0.810	0.420
NCV (m/s)	53.15 ± 5.64	55.08 ± 4.30	-1.962	0.052
Right ulnar	2.01 ± 0.50	2.00 ± 0.29	0.072	0.943
Distal latency (ms)	45.33 ± 19.64	43.15 ± 19.74	0.565	0.574
Amplitude (μV)	55.80 ± 4.60	55.98 ± 4.33	-0.208	0.836
NCV (m/s)				
Radial				
Distal latency (ms)	2.27 ± 0.84	2.30 ± 0.39	-237	0.813
Amplitude (μV)	16.26 ± 10.27	27.4 ± 13.20	-4.806	0.000
NCV (m/s)	51.75 ± 7.41	57.30 ± 4.53	-4.606	0.000
SENSORY				
Sural	2.90 ± 1.01	2.99 ± 0.81	-0.469	0.640
Distal latency (ms)	21.16 ±22.41	16.50 ± 11.60	1.331	0.186
Amplitude (μV)	42.48 ± 14.19	45.54 ± 8.86	-1.317	0.191
NCV (m/s)				
F wave				
Median				
Distal latency (ms)	23.20 ± 11.53	25.71 ± 4.91	-1.440	0.153
Peroneal				
Distal latency (ms)	43.80 ± 10.40	40.37 ± 8.00	1.882	0.063

NCV = nerve conduction velocity; ms = millisecond; uV = microvolt; m/s = meter/second; P<0.05 = statistically significant

Table 4. *Comparison of peripheral nervous system disorder rates before treatment and after 3 months of oral iron treatment*

Electrophysiological diagnosis	Before treatment, n (%)	After treatment, n (%)
Normal	38 (73.07)	50 (96.16)
Polyneuropathy	4 (7.69)	1 (1.92)
Carpal tunnel syndrome		
Right	4 (7.69)	0
Left	1 (1.94)	0
Bilateral	5 (9.61)	1 (1.92)

Comparison of peripheral nervous system disorder rates before treatment and after 3 months of oral iron treatment in IDA patients is summarized in Table 4.

IDA patients who were diagnosed with PNP electrophysiologically had paresthetic complaints such as pins and needles and numbness in fingers, burning and/or cooling in feet (n=4), and pain (n=1). Their neurologic examination revealed pain-heat sense loss in distal limbs (n=4), decrease in lower extremity deep tendon reflexes (DTR) (n=4), and decreased vibration sense in lower extremities (n=2). The major complaints of CTS patients were prominent numbness and pins and needles in the first three fingers at the lesion site. Moreover, neurologic examination findings were hypoesthesias in the distribution of the median nerve, and positive Phalen's and Tinel's tests (n=10).

DISCUSSION

Anemias affecting various organ systems are known as a heterogeneous group of disorders, and are described as serum hemoglobin levels below the reported normal values (5). While anemias present with decreased levels of serum Hb, which is involved in oxygen transport to the tissues, in clinical manifestation they can result in chronic tissue hypoxia (8,9).

Central and/or peripheral nervous system involvement of some anemias, such as pernicious anemia due to B_{12} deficiency, aplastic anemia, thalassemia, and IDA, is proven or still under investigation (14). IDA is one of the most frequent nutritional deficiencies and a common cause of anemia (8,15). IDA is mainly due to a low intake of dietary iron. Iron deficiency may have an effect on neurologic and intellectual functions, such as decreased motor activity, social interaction, and attention to tasks, especially in infants and adolescents. Moreover, IDA has well-known and reported effects on the nervous system including depression, decreased mental alertness, and disorders of sleep rhythm (14).

In our study, IDA patients underwent electrophysiological evaluation before oral iron treatment. The results of these initial electrophysiological evaluations revealed significant differences in the mean motor and sensory nerve conduction values of upper and lower extremities in the IDA patients when compared with age-matched controls.

Regarding these differences, bilateral median nerve motor and sensory nerve conduction values, radial nerve conduction velocities, and peroneal nerve motor distal latency, tibial nerve motor conduction velocity with sural sensory nerve conductions were statistically significant when compared with the control group ($P<0.05$). Prolonged peroneal nerve distal latencies were found and right median nerve and sural nerve sensory conduction velocities were slower than the reported reference normal values (11,12).

Our results revealed a predominantly sensory neuropathic process particularly in lower extremities. In support to our results that IDA leads to neuropathic processes, several previous studies have reported that iron has an important role in myelinogenesis *via* two possible mechanisms as a direct and an indirect pathway (16).

After 3 months of oral iron treatment, we found significant recovery in the motor (median nerve distal latency and ulnar nerve CMAP amplitudes bilaterally, tibial nerve conduction velocities), and sensory nerve conduction studies (median nerve SNAP amplitudes and nerve conduction velocities bilaterally, and radial nerve SNAP amplitudes and nerve conduction velocities) in our patients as compared with the pretreatment electrophysiological values, which in the pretreatment IDA patients were significantly different from those recorded in age-matched controls ($P<0.05$). These results suggested that this recovery may be due to iron replacement therapy.

Despite electrophysiological recovery in IDA patients according to the reported reference standards, some values were still significantly below the normal ranges of our control group. Because of these results, it has been considered that oral iron treatment longer than 3 months may lead to better electrophysiological and clinical recovery.

Similar to our study, Kabakus *et al*. demonstrated a statistically significant electrophysiological recovery in children with the diagnosis of IDA after 3-month treatment with 6 mg/kg/day oral ferrous sulfate (17).

We identified peripheral nerve involvement patterns by comparing pretreatment electrophysiological results in our IDA patients with the reported reference normal values. According to this comparison, 38 (73.07%) of 52 IDA patients were electrophysiologically normal, while four (7.69%) patients had PNP and ten (19.24%) patients had CTS, including 5 (9.61%) bilateral, 4 (7.69%) right-sided and 1 (1.94%) left-sided CTS.

When compared with the control group, the electrophysiological values of pretreatment IDA patients with the diagnosis of PNP revealed statistically significant slowness bilaterally in sensory ulnar and radial nerve conduction velocity, while no electrophysiological response could be obtained from the sural nerve stimulation. Furthermore, there were statistically significant prolonged peroneal and tibial motor distal latencies with slowed nerve conduction velocities in pretreatment IDA patients with the electrophysiological diagnosis of PNP as compared with age-matched controls ($P<0.05$).

Slowness in the left median nerve and radial nerve, and bilaterally in the ulnar nerve sensory conduction velocities, prolonged peroneal and tibial motor distal latencies with slowed nerve conduction velocities, which were statistically significant features of IDA patients with the diagnosis of PNP before treatment, were also abnormal according to the reported reference normal values (12). In addition, the lack of sensory sural nerve response was also a pathological finding relative to the reference normal values ($P<0.05$).

In contrast to the study by Kabakus *et al.* (17) revealing a polyneuropathy pattern affecting predominantly motor nerves in children with IDA, we determined a sensorimotor polyneuropathy process affecting predominantly sensory nerves in adults with IDA.

In the IDA patients with CTS identified electrophysiologically, there was a statistically significant prolongation of the median motor and sensory distal latencies bilaterally with decreased CMAP and SAP amplitudes and slowed nerve conduction velocities ($P<0.05$).

We found significant recovery in four of the five PNP and nine of the ten CTS patients with fully normal electrophysiological values. This could be due to iron replacement of intracellular enzymes or recovery from anemia, or both. Several previous studies have reported that iron therapy in children with IDA has been shown to replace intracellular iron-containing enzymes within 24 hours and to cause improvements in neuropsychiatric symptoms (14,17,18). The recovery observed in peripheral neuropathy findings with iron therapy may be related to the re-establishment of normal iron levels of enzymes, especially monoamine oxidase enzyme (MAO) (14).

In our study, one PNP and CTS subject each that were older than the mean age of the study population, showed no electrophysiological recovery after iron treatment (CTS and PNP patients aged 60 and 55, respectively). This result suggested that old age may be a factor affecting therapeutic response and/or recovery rate.

CONCLUSION

Eventually, we determined the association between neuropathic processes (PNP and CTS) and IDA in adulthood. Moreover, we found that these neuropathic symptoms and findings were reversible with appropriate doses and durations of oral iron treatment. Because of these findings, it is important to emphasize the investigation of iron deficiency anemia as an etiologic factor when planning treatment for neuropathy patients. In cases of IDA presence, it would be beneficial to treat IDA with iron replacement before applying other treatment options for neuropathy.

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