Reversal of Iron Deficiency Anemia-induced Peripheral Neuropathy by Iron Treatment in Children with Iron Deficiency Anemia

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Summary

The effects of iron deficiency anemia (IDA) on nerve conduction and efficiency of iron therapy were investigated by peripheral nerve-electrophysiological measurements. Eighteen children (10 boys, eight girls; mean age 31 ± 1.3 months) with IDA and 12 healthy children (six boys, six girls; mean age 29 ± 1.3 months) were enrolled into the study. Nerve conduction velocity was measured in the median and posterior tibial nerve. After nerve conduction values were determined in the patients and controls, 6 mg/kg/24 h ferrous sulphate was given orally to the patients for 3 months and nerve conduction velocity tests were performed again. Median/motor and sensory nerve conduction velocity and tibial/motor nerve distal-amplitute values of children with IDA were lower than for the control group ($p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively). With iron supplementation these values increased to the normal levels and even higher than control levels for some parameters. In correlation studies between whole blood parameters and nerve conduction velocity results, there was a correlation between median/sensory nerve conduction velocity values and serum iron levels. Additionally there was a correlation between some nerve conduction velocity values and age. In conclusion, the evidence from this preliminary study suggests that peripheral neuropathy may develop in children with IDA. Peripheral neuropathy symptoms in these patients may be improved by iron therapy.

Introduction

Iron deficiency is the most commonly encountered type of nutritional deficiency worldwide and a major cause of anemia in infancy and childhood.[1,2] The prevalence of iron deficiency anemia (IDA) in children is particularly high (around 10–25%) in the world and this prevalence is even higher among children, estimated to be as high as 50%, in under developed countries.[3,4]

It is well known that iron plays an important role in various metabolic and enzymatic processes. Iron deficiency anemia is mainly due to the low intake of bioavailable iron and is often associated with other conditions, including deficiency of vitamin A and folate, malnutrition, and infection. Iron deficiency may have an effect on neurological and intellectual functions, such as decreased motor activity, social interaction, and attention to tasks.[5] It is well known that iron deficiency causes alterations in many metabolic processes including mitochondrial electron transport, synthesis and degradation of neurotransmitters, and synthesis of proteins that have an impact on the functioning of the brain and other organs and systems.[6,7] A number of studies suggest that IDA, and even iron deficiency without anemia, affect attention span, alertness, and learning in both infants and adolescents.[1,3–5] Monoamine oxidase (MAO), an important enzyme, is known to play a crucial role in neurochemical reactions in the central nervous system. Iron deficiency causes a decrease in the activity of MAO.[8] It was found that experimentally-induced neuropathy in sheep caused a decrease in MAO activity.[9] These impairments may persist if the iron deficiency is not fully reversed.[10,11] These observations regarding IDA were the starting point for this study.

Measurement of nerve conduction using electromyography (EMG) is a frequently used non-invasive diagnostic method for the identification of various neuropathies. Low amplitude compound muscle action potentials and sensory action potentials with only a slight reduction of nerve conduction velocity indicates the existence of peripheral polyneuropathy.[12]

The aim of this study was to determine whether peripheral neuropathy was associated with IDA and whether iron treatment has any beneficial effects on this condition.

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Materials and Methods

Informed consent was obtained from parents of the patients and the protocol of this study was approved by the local Ethics Committee before commencing. Eighteen patients (10 boys, eight girls; mean age 31 ± 1.3 months, range: 25–42 months) with IDA and 12 healthy children (six boys, six girls; mean age 29 ± 1.3 months, range: 25–36 months) were enrolled into the study. It was confirmed that IDA findings were present in the patients. The patients with a hemoglobin value of less than 5 g/dl were excluded from this study due to possible other nutritional deficiencies (such as vitamins and minerals).[13] Due to technical difficulties of performing nerve conduction velocity measurements and available data in the literature for comparison, the patients' ages were limited to between 24 and 42 months.[14] All subjects were thoroughly examined clinically to rule out other causes of neuropathy.

In all subjects, blood samples were obtained in the morning when the subjects were hungry. In the control group, whole blood count, serum iron levels and nerve conduction velocities were determined only once. The other tests were carried out twice (before and after treatment) in the patients. Since it has been well documented that acute iron supplementation affects serum iron levels,[15] administration

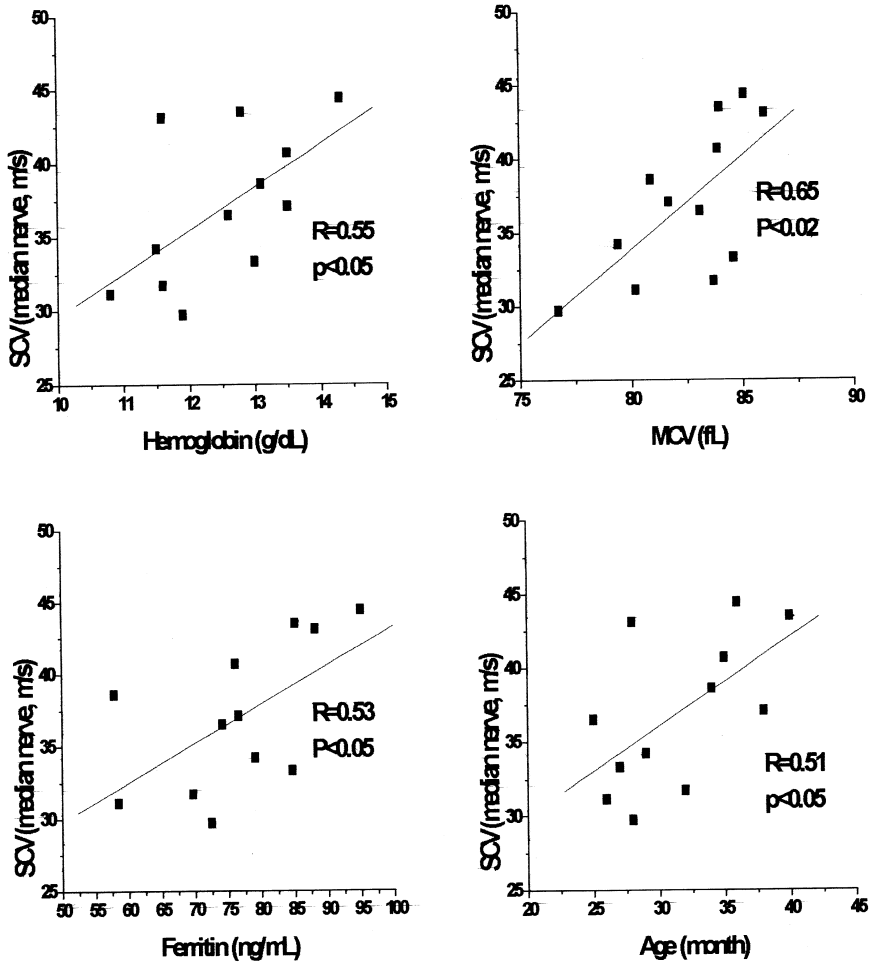


FIG. 1. Correlation between post-treatment values of sensory conduction velocity of median nerve and whole blood parameters (hemoglobin, MCV, ferritin), and age in 18 patients with iron deficiency anemia. The continuous line refers to the correlation between median nerve sensory conduction velocity and corresponding parameter. Regression coefficients and *p* values obtained from Pearson's test are given. SCV, sensory nerve conduction velocity; MCV, mean corpuscular volume.

of iron was terminated 48 h before the second laboratory analysis in the test groups. Whole blood counts were carried out by Diagnostics Advia 120 haematology analyser (Bayer, USA), serum ferritin by ACS: 180 Ferritin kits (Chiron/Diagnostics, USA), and serum iron and iron binding capacity by Randox kits (Randox, UK).

Electrophysiological assessments were carried out by a specialist neurologist. Nerve conductions were measured in the median and posterior tibial nerve as described by Moosa and Dubowitz[16,17] with a electromyography system (Dantec, Keypoint, Denmark). The median nerve was stimulated at the elbow and wrist and the compound muscle action potential was recorded using surface electrodes from the thenar muscles. The posterior tibial nerve was stimulated in the popliteal fossa and behind the medial malleolus. The compound muscle action potential was recorded from the flexor hallucis brevis muscle. The stimulus consisted of square wave impulses of 0.1 ms duration. Supramaximal stimulation was ensured by increasing the intensity of the

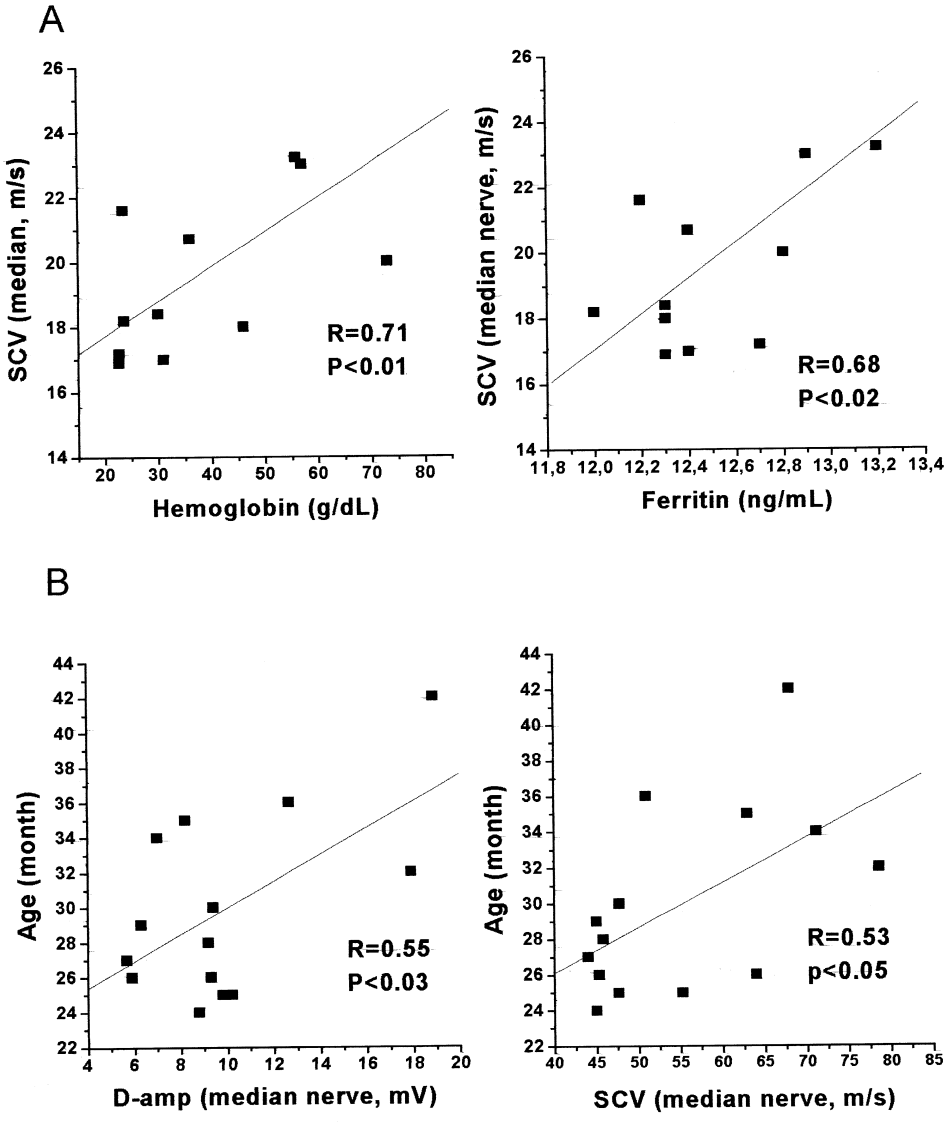


FIG. 2. Correlation between (A) median nerve SCV and hemoglobin and ferritin and between (B) age and D-amp and SCV in 12 healthy subjects. The continuous line refers to the correlation between median nerve sensory conduction velocity and corresponding parameter. Regression coefficients and *p* values obtained from Pearson's test are given. SCV, sensory nerve conduction velocity; D-amp, distal amplitude.

stimulus until no further increase in amplitude of the compound muscle action potential occurred. Two proximal and two distal compound muscle action potentials were recorded, and the latency was calculated from the stimulus artifact to the first well-defined negative peak of the compound muscle action potential. The difference in latency between the proximal and distal compound muscle action potentials was divided by the intercathode distance to give the conduction velocity in m/s. The intercathode distance was measured with a sliding metal caliper, the limb being held in the same position during stimulation. During measurement skin temperature was kept above 36.5ºC either by the help of an incubator in which the child was nursed or otherwise by means of a radiant heater. All compound muscle action potentials data were stored on a personal computer for later analysis.

After basal nerve conduction velocity studies were determined in the patients and controls, ferrous sulphate was orally administered to the patients only at a dose of 6 mg/kg/24 h for 3 months,[5] but not to the controls. After the 3-month period, peripheral nerve conduction tests were performed again in the IDA patients.

The results are presented as mean ± SEM. Data before and after therapy were analysed using Wilcoxon rank sum analysis. For comparison of data before therapy vs. controls and after therapy, Mann–Whitney *U*-test was used. A value of $p < 0.05$ was accepted as statistically significant. Relations between variables were studied by the Pearson correlation test.

Results

All physical examination results of children involved in this study were normal. Whole blood count, serum iron levels, and nerve conduction velocity findings in the test and control groups are shown in Tables 1 and 2, respectively. Distribution of age and sex of all children were similar ($p > 0.05$). Pretreatment serum iron levels of the patients were significantly different from those in the post-treatment period of the same group and also from the control group ($p < 0.05$). No significant differences were observed between the post-treatment values of the patient and the control group ($p > 0.05$). In children with IDA, pretreatment values of the median/motor nerve conduction velocity (except amplitude), median/sensory nerve conduction velocity and tibial/motor nerve distal-amplitude were lower than for the control group ($p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively). With iron supplementation these low values improved and became even higher than in the control group for some parameters. Nerve conduction velocity results in the control group showed a remarkable similarity to the values reported in the literature.[14,16,17]

Correlation between whole blood parameters and nerve conduction velocity values are given in Table 3. There was a correlation between median/sensory nerve conduction velocity values and serum iron levels. In addition, there was a correlation between some nerve conduction velocity values and age.

Discussion

The electromyographic nerve conduction velocity measurements in this study showed that children with IDA present mild peripheral neuropathy findings and these findings are reversible after oral iron administration. IDA is a disorder with various consequences. In addition to the iron containing enzymes of the central and peripheral nervous systems, several enzymes (such as monoamine oxidase, catalase and cytochromes) could be affected adversely by this process. Neurological and intellectual dysfunctions

TABLE 1
Values of serum iron, hemoglobin, hematocrit, and indices of red blood cells in children with iron deficiency anemia

Blood parameter	Pretreatment	Post-treatment	*p*
Hb (g/dl)	7.9 ± 0.3	12.3 ± 1.1	< 0.05
Htc (%)	26.1 ± 0.9	37.3 ± 3.1	< 0.05
MCV (fl)	58.4 ± 1.2	82.4 ± 2.9	< 0.01
MCH (pg)	17.8 ± 0.5	28.7 ± 2.7	< 0.01
MCHC (g/dl)	28.3 ± 0.7	31.7 ± 1.8	< 0.05
RDW (%)	19.2 ± 0.45	14.5 ± 1.7	< 0.05
SI (µg/dl)	24.1 ± 1.45	78.2 ± 18.7	< 0.01
SIBC (µg/dl)	354.2 ± 9.5	309 ± 38.6	> 0.05
Sat (%)	6.8 ± 0.5	24 ± 3.9	< 0.01
Ferritin (ng/ml)	2.8 ± 0.4	76.1 ± 19.9	< 0.01

Hb, hemoglobin; Htc, hematocrit; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red blood cell distribution width; MCV, mean corpuscular volume; Sat, saturation; SI, serum iron; SIBC, serum iron-binding capacity.

TABLE 2
Average values of nerve conduction velocities in children with iron deficiency anemia (pre- and post-iron treatment values) and healthy children (control)

Groups/Conduction velocities	IDA (pre-iron treatment)	IDA (post-iron treatment)	Control	Literature (ref. 14)
Median nerve (motor)				
D-lat	2.91 ± 0.07[f]	1.97 ± 0.11[a]	2.43 ± 0.1	2.15 ± 0.33
D-amp	3.14 ± 0.37[c]	9.38 ± 0.84[d]	10.17 ± 1.28	5.88 ± 2.51
CV	46.58 ± 2.77[a]	64.88 ± 2.69[d]	54.46 ± 3.42	52.7 ± 4.70
Amp (%)	15.67 ± 3.46	13.71 ± 2.65	11.75 ± 4.88	
Tibial nerve (motor)				
D-lat	4.05 ± 0.21[d]	2.85 ± 0.16	3.28 ± 0.28	2.49 ± 0.55
D-amp	6.27 ± 0.35[b]	9.90 ± 1.15	7.71 ± 0.35	6.42 ± 1.92
CV	41.52 ± 1.79	49.96 ± 1.11	46.72 ± 2.04	48.7 ± 4.86
Amp (%)	13.22 ± 3.51	8.64 ± 2.77	11.75 ± 2.43	
F	29.75 ± 1.45	22.72 ± 2.26	27.97 ± 1.97	
Median nerve (sensory)				
Lat	2.81 ± 0.08[e]	2.78 ± 0.33	2.41 ± 0.1	1.76 ± 0.17
CV	21.21 ± 0.92[a]	36.99 ± 1.48[f]	24.39 ± 1.05	19.51 ± 3.99
Amp (%)	12.93 ± 1.25	27.47 ± 3.12[f]	13.50 ± 0.89	

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ for comparison between pretreatment and control groups. [d] $p < 0.05$, [e] $p < 0.01$, [f] $p < 0.001$ for comparison between post-treatment and control groups.
D-lat, distal latency; D-amp, distal amplitude; Amp, amplitude; CV, conduction velocity; F, F-response; IDA, iron deficiency anemia.

observed in IDA are thought to be due to an insufficient level of MAO.[5,10]

In this study we identified a mild peripheral neuropathy particularly in the upper extremities affecting a motor nerve. Decreased MAO activity could be responsible for this neuropathy. El-Sebae, *et al.*[9] found decreased MAO levels in delayed neuropathy in a study performed on sheep. Nerves could also be affected by the IDA 'chronic ischemia' process. In addition, possible thrombocytosis due to IDA could contribute to this ischemic process.[18]

We found a significant recovery in nerve conduction velocity values after iron therapy. This could be due to iron replacement of intracellular enzymes or recovery from anemia or both. Iron therapy in children with IDA has been shown to replace intracellular iron-containing enzymes within 24 h and to cause improvements in neuropsychiatric symptoms, such as feeling well, a decrease in irritability, and an increase in appetite.[5,10] The recovery observed in peripheral neuropathy findings with iron therapy may be related to the re-establishment of normal iron levels of enzymes, especially MAO.

The finding of higher values of nerve conduction velocity after iron therapy in some patients could have been due to increased serum iron levels or treatment-induced activity in iron-containing enzymes. Since nerve conduction velocity measurements were performed 48 h after the end of iron therapy, it is unlikely to be the acute effect of iron on nerve conduction velocity.

The correlation between serum iron levels and median/sensory nerve conduction velocity of healthy children and patients may implicate the contribution of IDA to peripheral neuropathy. To our knowledge, the association between IDA and peripheral neuropathy in children has not been described before, and further research needs to be carried out for possible explanations. However, the present study is preliminary, the beneficial effects of iron supplementation in neuropathy should be studied in larger randomized groups.

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