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Clinical Trial of Iron Therapy on Psychomotor Function in Anaemic Women

P. C. ELWOOD,* M.D. ; DAFYDD HUGHES,† M.B., B.CH., D.P.M.

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Summary: A variety of aspects of psychomotor function were assessed in 47 women before and after iron therapy. These women, all of whom had initial haemoglobin levels below 10·5 g./100 ml., had been drawn from a population sample of 2,283 women seen at a haematological screening survey. There was no evidence of any beneficial effect of a rise in haemoglobin level on psychomotor function or on symptoms. Possibly this is because if an effect does occur it is unlikely to be apparent unless the haemoglobin level is very low. If this is true then anaemia is probably a rare cause of symptoms or impairment in psychomotor function in the community.

Introduction

The importance of iron deficiency in realistic terms of increased morbidity and impairment of function has not been fully established. In earlier studies its effect on symptoms and on cardiorespiratory function was examined (Cotes *et al.*, 1969; Elwood *et al.*, 1969). In this paper the effect of iron therapy on the psychomotor function of a population sample of anaemic women is examined.

Method

All the women aged 20 years and over who lived in a defined area in a Welsh mining valley were visited and invited to attend a haematological screening survey. A sample of venous blood was taken for estimation of haemoglobin level (as g./100 ml.) and packed cell volume (as %).

Women found to have haemoglobin levels below 10·5 g. were visited at home and asked about symptoms which might suggest the presence of a serious underlying condition; blood films were prepared to exclude a macrocytic anaemia. Investigation at hospital was offered where appropriate. They were then asked to co-operate in a study of the effect of iron therapy on a variety of simple performance tests. Those who agreed were given these tests at home, and then randomly allocated, in a ratio of 4:3, to iron (150 mg. Fe as ferrous carbonate daily) or given tablets of similar appearance which contained no iron. At the end of eight weeks' treatment a further sample of blood was taken and each of the performance tests repeated. All the women who were still anaemic were then given oral iron until their haemoglobin level was above 12 g.

* Member of Medical Research Council Epidemiology Unit, Cardiff.
†On Scientific Staff, Medical Research Council, Cardiff.

The performance tests were chosen to cover a range of psychomotor functions, from an almost pure test of intellectual function to a simple test of manual dexterity. They were administered by two trained observers who were blind to the treatment given. The conditions under which the tests were done and the instructions given to each subject were standardized as carefully as possible, and the results of the first series were unknown to the observers when the tests were repeated at the end of treatment.

(1) *Serial Sevens.*—The subject is instructed to subtract seven repeatedly from 100, stating the answer at each subtraction. The time taken for 14 subtractions, regardless of errors and the number of errors, is recorded. A different starting number was used on the second test to minimize the learning effect. This is a pure test of intellectual function involving concentration, arithmetic reasoning, and short-term memory.

(2) *E Test.*—A page of printed text is presented to the subject and she is told to cross out every letter "e" as quickly as possible. After one and two minutes the subject is encouraged to go more quickly. The number of E's crossed out in three minutes is recorded. This test involves vigilance, concentration, and a degree of dexterity.

(3) *Maze Test.*—This test is a boldly printed spiral maze (Gibson, 1964). The subject is asked to draw a line which does not touch the edge or any of a number of obstacles in the path of the maze. At 15-second intervals the subject is told to go more quickly. The time taken to complete the test is recorded and the errors where the line left the maze are scored. Comparisons are made in terms of this score as a regression on the time taken. This test requires attention, concentration, and agility in motor function.

(4) *Card Sorter.*—This is a modified form of a test used in a Himalayan expedition in 1960-1 to detect the effect of anoxia on performance (Pugh, 1962). Playing-cards are sorted by suit into appropriate sections in a box for six minutes after a practice run for one minute. If after a card has entered the box there is a delay of more than a preset interval of 1·5 seconds, this is detected electronically and a loud clicking noise is emitted until the next card enters. The number of such delayed responses, and their total duration in excess of 1·5 seconds, are recorded and are here referred to as "number" and "time" respectively. After one, three, and five minutes of the test the subject is encouraged to go more quickly. This test involves sustained repetitive decision making, co-ordination, and manual dexterity. As it is a protracted test, and was the last test administered, it is likely that subjects susceptible to fatigue will perform badly.

(5) *Peg Board.*—Forty-eight small wooden pegs, each in a hole in a board, are taken out one at a time, turned upside down, and replaced. The time in seconds to complete this is measured. This is a simple test of manual dexterity.

Finally, the severities of six symptoms commonly attributed to anaemia were graded by a method based on that devised by Ingham (1965). Each woman was also asked to make an assessment of her condition by marking the position she supposed her general state of health to occupy on a continuous 20-cm. line, one end of which was said to represent perfect health and the other severe ill-health. The change in the position indicated at the beginning and at the end of the trial was measured.

Results

There were 2,283 women resident in the defined area, 2,049 (90%) being seen at the screening survey. Of these, 53 had haemoglobin levels below 10·5 g. Four were unsuitable for inclusion in the trial because of serious illness, and two had later to be omitted from the trial because of inadequate co-operation. Forty-seven women therefore completed the trial. A few did not complete all the tests, either because of occasional technical difficulties with a test or because of lack of co-operation. This last usually occurred with the "serial sevens" test, which proved to be rather unpopular.

The changes in the performance tests during the trial are shown in Table I. The subjects have been divided into three groups which correspond to their changes in haemoglobin level during the trial. In none of the tests are the differences between the means significant (at $P<0.05$). No test shows the expected gradient, the greatest improvement being in those who, on average, showed the largest rise in haemoglobin level, and the smallest improvement in those who showed, on average, no change in haemoglobin level.

The mean changes in symptoms and in self-assessment are shown in Table II. Again there is no evidence of benefit of iron therapy which is statistically significant for any symptom, nor is there any evidence of a consistent trend in the pattern of changes in all the symptoms.

Discussion

Two groups of hypotheses have been advanced to explain certain effects which are generally believed to occur in iron deficiency. One group is concerned with the oxygen transport. Undoubtedly circulating haemoglobin can be lowered sufficiently to cause symptoms and effects on function, but the level below which effects occur in otherwise healthy subjects is unknown. It is probably around 7 g. (Brannon *et al.*, 1945; Duke and Ablemann, 1969) or 8 g. (Elwood *et al.*, 1969). The other group of hypotheses is concerned with an effect of iron deficiency on tissue enzymes. The activity of certain enzyme systems is altered in iron deficiency (Beutler, 1959; Jacobs, 1961; Dagg *et al.*, 1966). These changes have been suggested as a cause of certain effects, including symptoms (Baird *et al.*, 1961) and in particular fatigue (Beutler *et al.*, 1960).

In the present study a wide range of possible effects of iron deficiency have been examined. Though the functions examined in each of the tests cannot be defined in terms of specific psychomotor mechanisms which may be affected by changes in oxygen transport or tissue enzyme function, probably mechanisms of both these kinds are involved in the tests used. These were chosen to sample psychomotor function in areas where it was considered most likely that an impairment of function by iron deficiency would be apparent. Thus the assessment of function covered a wide range from intellectual to motor functions, and the five tests were administered without a break to induce some degree of fatigue.

The results show no evidence of a significant difference in the change in the performance of the subjects given iron and those given placebo tablets. It could therefore be concluded that iron has no beneficial effect on psychomotor function in iron deficiency. The absence of a change in symptoms in this and in other studies (Elwood and Wood, 1966; Elwood *et al.*, 1969); supports this conclusion. There are, however, other explanations of the findings. Firstly, as the tests examined limited areas of psychomotor function they may have been inappropriate to detect changes due to iron deficiency. This is improbable. A wide range of function was assessed, and it seems unlikely that an improvement would not have been detected by at least one of the tests.

The second possibility is that the tests were not sensitive enough to detect an improvement. This hypothesis implies that if an improvement did in fact occur in our study it was very small. An estimate of the sensitivity of the tests used can be obtained from the size of the standard errors in Table I. The changes in those given no iron largely represent the effect of learning, and for four of the five tests it is significantly larger than its standard error. It seems unlikely that tests which can detect a learning effect could miss an important beneficial effect of iron therapy.

Finally, on the other hand the subjects might not have been sufficiently deficient in iron for an effect of treatment to be detected. This seems to us a most reasonable explanation of the results. If this explanation is true, however, it implies that anaemia is a rare cause of symptoms or impairment of psychomotor function in the community. In the population sample screened for this study the percentages with haemoglobin levels below 10·5, 9, and 8 g. respectively were only 3, 0·7, and 0·1.

TABLE I.—*Mean Changes (±S.E.) in Performance Tests during Trial in Subjects Given No Iron and in Subjects Given Iron, Divided into Two Groups by Change in Haemoglobin Level with Treatment*

Tests	Mean Changes in Test		
	Given No Iron	Given Iron (Change in Hb under 2 g.)	Given Iron (Change in Hb over 2 g.)
No. of subjects	21	12	14
Mean Hb change	0·0 g.	0·9 g.	3·2 g.
Mean P.C.V. change	0·3%	3·2%	8·4%
Serial sevens. Time	− 3·8± 1·3	− 1·5± 2·0	− 3·4± 1·8
E test. Number	6·5± 3·2	− 3·8± 4·8	1·0± 2·9
Maze. Error	2·6± 2·9	− 9·5± 3·7	− 5·1± 3·4
Card sorter Number	− 7·9± 3·9	17·5±11·9	− 5·0± 5·6
Card sorter Time	−134·7±29·8	−90·2±61·9	−165·8±53·0
Peg board. Time	− 18·4± 5·6	−17·0± 6·4	− 9·2± 8·1

Note: For E test and card sorter (number) a positive change indicates improvement; for all other tests a negative change indicates improvement.

TABLE II.—*Mean Changes (±S.E.) in Symptom Grades with Treatment (Groups of Subjects Defined in Table I)*

Symptom	Mean Changes in Symptom Grades		
	Given No Iron	Given Iron (Change in Hb under 2 g.)	Given Iron (Change in Hb over 2 g.)
Headache	−0·3±0·3	−0·2±0·6	−0·7±0·6
Breathlessness	0·1±0·2	−1·2±0·6	−0·1±0·5
Dizziness	0·0±0·2	−0·3±0·3	−0·9±0·4
Fatigue	−0·7±0·4	−1·1±0·5	−1·5±0·5
Palpitations	−0·2±0·5	−0·6±0·5	−0·7±0·3
Irritability	−1·1±0·4	−0·6±0·5	−0·7±0·6
Self-assessment	0·6±0·2	0·7±0·4	0·6±0·3

Note: For each symptom a negative change implies improvement.

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