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Reversible Cognitive Decline During High-Dose α-Interferon Treatment

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POUTIAINEN, E., L. HOKKANEN, M.-L. NIEMI AND M. FÄRKKILÄ. *Reversible cognitive decline during high-dose α-interferon treatment.* PHARMACOL BIOCHEM BEHAV 47(4) 901-905, 1994.—The cognitive effects of high-dose human leukocyte α-interferon (IFN-α) treatment were evaluated among 15 patients with the newly diagnosed spinal form of amyotrophic lateral sclerosis (ALS). To confirm the earlier findings showing reversible effects on cognitive performance and to exclude confounding effects, a randomized blinded placebo controlled study was conducted. Twelve patients with continuous intravenous IFN-α-infusion treatment over five days and 3 placebo control patients were neuropsychologically evaluated. The neuropsychological examination included tests of intelligence, memory, complex mental processing, visuoconstructional skills, writing, and calculation. A clear difference in the performance profiles of the placebo and the IFN-α-treated patient groups was detected: The IFN-α group showed significant deterioration during treatment in the digit span backwards task, logical verbal memory task, calculation ability, and writing time, while improvement was seen after treatment. Concomitant fever did not explain the findings. In the placebo group an improvement indicating a learning effect in the three consecutive measurements was found. The reversible cognitive deterioration indicates a clear CNS effect during the IFN-α treatment.

Interferon Cognitive changes Neurotoxicity ALS

SINCE the earliest studies on human leukocyte alpha interferon (IFN-α), neurotoxicity-like drowsiness, confusion, EEG changes, and tiredness have been reported (10,13,14). Moreover, cognitive impairment and symptoms of reversible dementia have been described in connection with high-dose intravenous IFN-α treatment (7,12). IFN-α-induced changes in visually and auditively evoked brain stem potentials have also been described (4). All the described changes have been temporarily related to IFN-α treatment and have been reversible. Interferon has been shown to cross the blood-cerebrospinal fluid barrier in monkeys (6) and humans (3), at ratios 1 : 20 to 1 : 50. In neuropsychological studies, loss of initiation of performance, slowing of mental capacity, memory disturbances, and also motor and visual slowing have been recognized both in short-term high-dose treatment and long-term low-dose treatment (4,9,12).

The aim of the present study was to confirm in a controlled randomized and blinded manner the earlier findings of cognitive effects of intravenous high-dose IFN-α treatment. In addition, we wanted to exclude confounding effects such as prior cognitive deficits (like in brain metastases or cancers). Therefore we decided to use patients with amyotrophic lateral sclerosis (ALS), which affects the motor neurons in the spinal cord but does not cause cognitive changes primarily.

PATIENTS AND METHODS

Twenty-one patients with ALS (14 males, 7 females) were initially enrolled. The diagnosis of ALS was based on clinical follow-up and electromyography (EMG) after all other possible diseases were excluded. Patients did not have any other CNS diseases. Only newly diagnosed patients with initial spinal form of ALS affecting more than one limb, good general condition, and less than 75 years of age were included (3). Informed consent was obtained from all patients, and the study was approved by the Ethical Committee of the hospital.

This was a randomized blinded study with alpha interferon as the active drug or albumin solution as placebo. The patients were randomly selected for either an IFN group (n = 16) or a placebo group (n = 5) single-blinded, so that only one of the whole staff (M.F.) was aware of the nature of the infusion. For ethical reasons we decided to randomize only six patients to placebo group, but only five were enrolled. The IFN vials and placebo vials were indistinguishable, the infusion fluid

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TABLE 1

DEMOGRAPHIC CHARACTERISTICS OF THE PLACEBO AND HIGH-DOSE α-INTERFERON-TREATED AMYOTROPHIC LATERAL SCLEROSIS PATIENTS (mean ± SD)

	Placebo (n = 3)	IFN-α (n = 12)	t Value*	p
Age (years)	52.3 ± 8.1	49.4 ± 11.8	0.50	NS
Years of education	9.7 ± 1.2	11.3 ± 2.7	−1.62	NS
General intelligence†	105.3 ± 14.8	115.4 ± 11.3	−1.10	NS

*Two-tailed t test. †Verbal Intelligence Scale of the Wechsler Adult Intelligence Scale.

being the same in both groups (2000 ml, 0.9% sodium chloride, and 5% glucose). All patients were treated with five days of continuous IV infusion and were hospitalized during the treatment. The IFN-α group patients received 100 million IU/day during the first two days and 200 million IU on the following three days.

The neuropsychological testing program was designed on the bases of previous data collected in our department on both ALS patients (3) and patients with small cell lung cancer (SCLC) treated with IFN-α (12). Neuropsychological examination included tests of memory and concentration—Mental Control, Digit Span, and Logical Memory tasks of the Wechsler Memory Scale (WMS) (16) and calculation ability; tests of complex mental processing—Naming and Interference tasks of the Stroop test (5); a task of visuoconstructional skills—Copying a Cube; and Signature Writing. We also monitored the level of general orientation through an extended version of the WMS Orientation. The examination was performed at baseline before treatment (day 0), on the last day of the treatment (day 5), and three days after the treatment (day 8). According to the earlier studies, it was assumed that the peak of the effect would appear around the fifth day. Thus, we carried out statistical comparisons (analysis of variance for repeated measures) using separate analyses between days 0 and 5 and days 5 and 8.

All subjects completed the neuropsychological examination at entry (day 0). One patient was excluded from the cognitive analysis because he was unconscious due to interferon on day 5. An additional 2 patients (1 IFN-treated and 1 control patient) were excluded because they became apathetic and aggressive and refused to perform the tests at day 5. Furthermore, the day 8 examination was not available for 3 subjects: 2 IFN-treated patients refused to complete the examination and 1 control patient was sent home because of a good general condition after the treatment period. Thus, 15 patients (12 with INF-α treatment and 3 with placebo) were included in the analysis of neuropsychological data. Finally, there were no differences between the 12 INF-α-treated and 3 placebo patients in mean years of age, education, or the general intelligence estimated by the Information and Similarities subtests of the Wechsler Adult Intelligence Scale (WAIS) (17) (Table 1).

Initially the routine laboratory tests as well as the electrocardiogram (ECG) and chest X-ray were normal in both groups. Blood pressure, respiration frequency, and pulse were monitored every fourth hour in all patients and were normal. Neurotoxic and haematological side effects (temporary leucopenia and thrombopenia) of high-dose IFN-α treatment were observed in all patients receiving interferon, and in seven patients the planned dosage was reduced because of tiredness, leukopenia, or both (leukocyte count below 2.0). The mean cumulative tolerated IFN dose was 510 million IU during the

TABLE 2

PERFORMANCE OF THE IFN-α TREATED PATIENTS IN DIFFERENT NEUROPSYCHOLOGICAL VARIABLES AT DAY 0, DAY 5, AND DAY 8 (mean ± SD)

		Treatment		
Cognitive Variable	n*	Before Day 0	During Day 5	After Day 8
WMS/20-1 Counting†	11	11.5 ± 2.9	14.8 ± 7.7	12.1 ± 3.8
WMS/Counting by 3s†	11	29.5 ± 12.8	37.1 ± 24.5	31.3 ± 14.3
WMS/Digits Backwards	12	4.7 ± 1.4	3.8 ± 1.5	4.5 ± 0.5
WMS/Logical Memory	12	13.0 ± 3.9‡	10.4 ± 3.4	10.6 ± 3.4
Stroop Naming†	5	61.4 ± 9.2	62.4 ± 12.8	60.2 ± 12.0
Stroop Interference†	6	129.5 ± 42.5	127.7 ± 60.1	110.7 ± 46.1
Copying a Cube†	6	37.5 ± 30.9	58.8 ± 47.5	53.7 ± 53.6
Calculation (max. 8)	11	7.5 ± 0.9‡	6.7 ± 1.4	7.2 ± 1.0
Signature Writing†	6	8.7 ± 6.3‡	12.6 ± 6.6‡	14.0 ± 7.3

*Variability of group sizes still remained in analysis because we used only patients that completed all three examinations in individual tests. †Time in seconds (lower values indicate better performance). ‡$p < 0.05$ between adjacent days.

TABLE 3

PERFORMANCE OF THE PLACEBO-TREATED PATIENTS IN DIFFERENT NEUROPSYCHOLOGICAL VARIABLES AT DAY 0, DAY 5, AND DAY 8 (mean ± SD)

Cognitive Variable	n*	Treatment: Before Day 0	During Day 5	After Day 8
WMS/20-1 Counting†	3	14.3 ± 5.9	15.0 ± 4.0	15.0 ± 5.3
WMS/Counting by 3s†	3	33.3 ± 13.7	28.3 ± 5.9	29.7 ± 16.5
WMS/Digits Backwards	3	3.7 ± 1.5	4.3 ± 2.1	4.0 ± 1.0
WMS/Logical Memory	3	14.3 ± 3.8	9.5 ± 4.3	9.7 ± 1.3
Stroop Naming†	3	76.3 ± 30.0	69.7 ± 17.8	66.7 ± 21.5
Stroop Interference†	3	131.3 ± 56.1	106.7 ± 42.1	99.3 ± 37.9
Copying a Cube†	3	63.0 ± 34.5	46.0 ± 23.3	39.3 ± 18.0
Calculation (max. 8)	3	6.0 ± 1.0	7.3 ± 0.6	7.0 ± 1.0
Signature Writing†	3	7.3 ± 1.5	6.0 ± 1.0	6.0 ± 1.4

*Only complete cases included. †Time in seconds (lower values indicated better performance).

treatment. All IFN-treated patients and one control subject had an occasional fever during the treatment period. Furthermore, seven IFN-treated patients had slight fever ranging from 37.1 to 38.6°C (mean = 37.2) during the neuropsychological examination at day 5.

RESULTS

In the IFN-α group a statistically significant ($p < .05$, ANOVA for repeated measures) cognitive deterioration was detected in the Logical Memory task of the WMS, Calculation ability, and Signature Writing time during the high-dose treatment (days 0 vs. 5) (Table 2). A similar but statistically nonsignificant trend was also observed in most of the other tests, and in the Digit Span Backwards task of the WMS the difference was nearly significant ($p < .06$). After discontinuation of the IFN-α treatment (days 5 vs. 8), improvement occured in all tests except Signature Writing time. The placebo group members improved their cognitive performance all through the treatment although no statistically significant changes

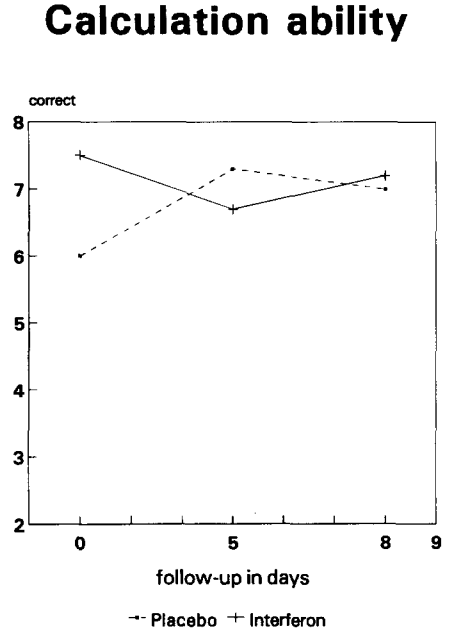

FIG. 1. Significant ($p < 0.05$) deterioration in calculation ability after five days of high-dose IFN-treatment followed by an improving trend at day 8 (three days after discontinuation of the treatment). In contrast to that, the placebo group showed an improving trend. The difference in the trends of the two groups reached a statistical significance ($p < 0.02$).

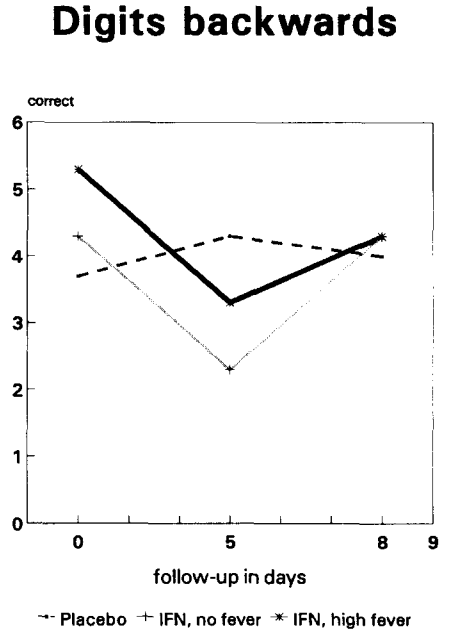

FIG. 2. The impairment of the performance in the Digit Span Backwards test of the WMS was similar in the IFN-treated group with high fever ($n = 3$) and the IFN-treated group without fever ($n = 3$), while members of the placebo group ($n = 3$) improved their performance. The difference between the placebo group and the two IFN-groups in separate analyses was significant ($p < 0.05$).

emerged (Table 3). Only in Logical Memory and 20-1 Counting time tasks of the WMS was no improvement detected. In Calculation ability the difference between trends of the IFN-α-treated and placebo groups was statistically significant, $F(1, 10) = 7.35, p < .02$, ANOVA (Fig. 1).

To estimate the possible deviation of results due to dropouts (four IFN-α-treated and two placebo controls) we evaluated the data about the examinations they completed. The two patients (one IFN-α-treated and one control patient) who refused to complete the tests at day 5 performed worse on cognitive tests at day 8 when compared with the performance at day 0. Furthermore, of the three patients who did not complete the day 8 examination, in two IFN-α-treated patients no differences between the examinations at day 0 and day 5 were found, while a control patient improved his performance during the treatment period. One patient completed only day 0 examination due to unconsciousness during the treatment.

To determine if fever in seven IFN-α-treated patients at day 5 might have accounted for the results of cognitive performance we compared the results of examinations at days 0 and 5 in the three IFN-α-treated patients with the highest fever (temperatures 38.6°, 37.8°, and 37.5°C), in three similar patients without fever at day 5 (temperatures below 37.0°C), and in the placebo group. In the Digit Span Backwards test, the Copying a Cube task, Calculation ability, and Signature Writing time the same declining trend was found in both of the IFN-α-treated groups, while controls improved their performance between days 0 and 5. In the Digit Span Backwards task of the WMS the difference in performance of the two IFN-α-treated groups and placebo group was significant, $F(2, 6) = 6.40, p < .03$ (Fig. 2). In pairwise comparison the control group differed from both the high-fever IFN group and the no-fever IFN group ($p < 0.05$). Only in the two Stroop tasks and in the Counting by 3s task of the WMS Mental Control subtest did the decline in performance at day 5 seem to be explained by the fever, since the performance declined in patients with fever, while the IFN-α-treated patients without fever shared the same improving trend with the placebo group. In the Interference task of the Stroop test this interaction was significant, $F(2, 4) = 10.91, p < .02$. With Logical Memory and the 20-1 Counting task of the WMS Mental Control the declining trend was found in all three groups.

DISCUSSION

In this placebo controlled study, cognitive alteration after five days of high-dose IFN-α treatment occurred in newly diagnosed ALS patients. Deterioration was significant in cognitive performance involving memory and concentration (Logical Memory task of the WMS and Calculation ability) and Signature Writing time. All the other tests, except the Stroop Interference task, also showed a declining trend during the IFN-α treatment. This deterioration, however, was reversible, since the improvement was observed in examination after three days of discontinuation of the treatment. Thus, our results are similar to earlier findings of ALS patients (7,8) and cancer patients (renal cell carcinoma, small cell lung cancer) receiving high-dose IFN (1,2,4).

The existence of ALS-related cognitive deficits (11) was controlled by including only newly diagnosed patients with the spinal form of ALS. Moreover, general intelligence was estimated and found to be within normal range in both the IFN-α-treated and placebo groups, and no group differences emerged. The patients remained blinded to the study design, although the professional staff may have recognized some side effects of IFN. The neuropsychologist who performed the testing was unaware of the medical records of the patients.

Unlike the IFN-α-treated patients, the placebo group showed an improving trend, typical to repeated testing, both during the five days of albumin solution infusion and after three days of discontinuation of the treatment. This expected learning effect of the placebo group suggests that the cognitive alteration of IFN-α-treated patients could not be explained by the hospitalization or medical care of the patients.

In contrast to the general trend, in the test of Logical Memory of the WMS the performance declined during the treatment period in both groups, and no improvement occured after discontinuation of the treatment. This may be explained by the fact that in each examination different passages with possibly differing levels of difficulty were used. The decline in the Signature Writing time of the IFN-α-treated group still three days after the treatment period may indicate a prolonged effect of interferon on tasks requiring fine motor control.

Three IFN-treated patients were unable to participate in tests due to neurotoxic side effects, and so perhaps the most severe cognitive defects were not seen at all. In the crude analysis of their incomplete test performance no improvement occured, which supports our conclusions. The fact that two of the control patients also had to be excluded in the study due to missing data (one refused on day 5 and one insisted on returning home prematurely) reflects the difficulty of this kind of trial even under the placebo condition.

In earlier studies of IFN effects on cognitive performance the concomitant fever has been frequently reported (15). However, the possible interaction of fever and cognitive changes has not been previously discussed. Seven of our 12 IFN-α-treated patients had at most a slight fever on the day 5 examination, which might explain the declined cognitive performance on that day. However, after controlling the possible effect of fever over the cognitive performance it appeared that the declining trend, particularly in the Digit Span backwards test of the WMS and also in the Copying a Cube test, Calculation ability, and Signature Writing time during the IFN-α treatment period, could not be explained by the concomitant fever. Thus, confounding effects such as fever, IV infusion, or hospitalization have not affected the results.

In conclusion, we believe that the reversible deterioration of cognitive performance in IFN-α-treated ALS patients, and a linearly improving trend in the placebo group with an otherwise similar medical situation, indicate a clear CNS effect during a high-dose IFN-α treatment.

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