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PSYCHO-ENDOCRINOLOGICAL REACTIONS IN FEMALE RELATIVES OF CANCER PATIENTS

Effects of an activation programme

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Abstract

Psychiatric grief reactions after the loss of a close relative are associated with endocrinological reactions, in particular elevated plasma cortisol. In the present study it was tested if a psychosocial intervention programme for relatives to cancer patients affects the reaction patterns. Thirty-six female relatives in the intervention programme were compared with 36 relatives only subjected to a routine programme. Eighteen of the relatives in the intervention programme and 17 in the routine programme experienced the death of the patient during the study period. Systematic psychiatric observations and analyses of the plasma levels of cortisol and prolactin were made approximately once a month. During the treatment period the psychiatric scores did not differ between the groups, but the prolactin levels tended to be lower in the intervention group ($p=0.06$). During the terminal phase preceding the patient's death the plasma cortisol levels were significantly elevated in the intervention group but not in the routine group. At examination one and two months after the death of the patient the mental exhaustion scores were significantly lower in the intervention group. The findings are consistent with the hypothesis that grief is activated by the intervention and that the active mourning may have prophylactic value to the relatives after the death of the patient.

Key words: Neoplasms; cancer, relatives, endocrinological reactions, psychological reactions, bereavment, grief.

Previous studies have shown that psychiatric grief reactions after the loss of a close relative are associated with endocrinological reactions, particularly elevated plasma cortisol, and also that the magnitude of the plasma cortisol is depending on the type of coping (6). It was expected that a programme for activation of relatives could affect not only the grief process but also the endocrinological reaction patterns. In the present study female relatives of cancer patients were observed during a treatment period organized by the oncological ward and also during the terminal care period and one and two months following the death of the patient.

The two groups of relatives were observed under the following conditions:

Comparison group. Only customary attention was given to the relatives in this group. It should be pointed out that the oncological ward at the Karolinska sjukhuset has an advanced programme for taking care of the patient's psychosocial needs. However, previously no particular attention has been paid to the psychosocial needs of the relatives.

Two subgroups of relatives were recruited to the comparison group. Firstly, in one of the ward (A) which later became the experimental ward—with main emphasis on treatment of cancer of the oesophagus or the urogenital organs—relatives to patients recruited during the period January to August 1984. Secondly, relatives to patients recruited from other wards during the period January 1984 to April 1985.

The relatives in these two subgroups were comparable with regard to sex and age and also regarding severity of the patient's disease. They are therefore analysed as one group in the following presentation (comparison group) (Tables 1, 2).

Activation group. The activation programme started in August 1984 and lasted until April 1985. The ward personnel improved their first contacts with the patients' rela-

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tives. They were offered the opportunity of taking part in the care of the patient at the hospital. Relatives who accepted were provided with free food and had the opportunity of staying overnight. If the patient and the relative agreed about home care, they could maintain telephone contact with the ward. The ward personnel gave more detailed and continuous information to the relatives than in the routine programme. In order to improve the contact with the primary care the district nurses were invited to the hospital in order to meet the patient, the relative and the ward personnel before the patient was discharged. Relatives were invited to a group meeting, at which representatives for the different professional groups described their duties in the ward. The ward physician presented the tumour diseases in the ward and how to treat them. A nurse described common psychological reactions of patients and relatives, caused by the disease. The whole activation programme was carried out with resources already available in the department.

The present study was designed for evaluation of possible effects of the total programme but not of its individual components. In the evaluation, the 'intention to treat' principle was used, i.e. all the relatives who were offered the activation programme were included in the activation group, regardless of degree of actual participation.

This study has been approved by the regional committee of medical ethics at the Karolinska Institute.

Material and Methods

The study took place at the Department of Clinical Oncology, Karolinska Sjukhuset, Stockholm. At the department all kinds of non-surgical cancer therapy were given such as cytostatic treatment, radiation therapy and pain relieving and supporting treatment. Close female relatives (wives, sibilings or children) of patients treated for cancer were asked to participate in the study. Good knowledge of the Swedish language was required. Persons with serious illness and age exceeding 80 years were not included. Relatives were recruited with the intention to make the activation and the comparison groups comparable with regard to age, severity of the patient's illness and time of the year for the examination. Of 137 relatives who were offered to participate in the study 96 accepted. In the comparison group 34 per cent and in the activation group 26 per cent did not participate. Twelve relatives interrupted their participation after the first contact (5 in the comparison group and 7 in the activation group). The results from these persons are not included in the study. Twelve persons participated on one occasion before the patient died (6 in the comparison group and 6 in the activation group). The results from these persons are included in the study of relatives of patients who died during the study.

Women who were pregnant, breast feeding or using contraceptive pills were excluded from the endocrinological analysis. Interestingly, in this sample of mainly middle-aged women none was using psychotropic drugs during the periods of study.

Table 1

Age of patient's relative, severity of patient's illness at the start (Karnofsky index) and median month of examination of the activation and comparison conditions (surviving and dying patients). (Only relatives with at least two observations before patient's death)

	No. of subjects	Age		Karnofsky	
		Mean	Range	Mean	Range
Comparison	36	51	24–77	71.7	50–90
Activation	36	52	21–72	69.5	40–100
	No. of subjects	Jan.–March	Apr.–June	July–Sept.	Oct.–Dec.
Comparison	36	6	17	10	3
Activation	36	11	10	6	9

Table 2

Age, severity of patient's illness (Karnofsky index) and median month of examination of activation and comparison conditions of relatives of patients who died during the study (including relatives with only one observation before patient's death)

	No. of subjects	Age		Karnofsky	
		Mean	Range	Mean	Range
Comparison	17	55.3	26–73	68.2	50–80
Activation	18	49.0	24–72	63.0	40–80
	No. of subjects	Jan.–March	Apr.–June	July–Sept.	Oct.–Dec.
Comparison	17	5	9	3	
Activation	18	8	5	1	4

The groups were thus comparable with regard to age and severity of illness. The proportion of patients who died was also comparable—17/36 in the comparison condition and 18/36 in the activation condition.

Psychiatric observations regarding anxiety, depression and mental exhaustion were made on each occasion (intervals between 3 and 4 weeks) by means of a standardised procedure according to Holland and Sgroi (2, 7). Three observers were trained together. The interrater reliability was tested. For the three dimensions, anxiety, depression and mental exhaustion the reliability coefficients were 0.82, 0.79 and 0.91 respectively.

Blood samples were drawn on each occasion. Time of day for the venipuncture was not strictly comparable between the two groups. There was a group difference of approximately 2 h in the median time of venipuncture. Each subject, however, had a constant time of venipuncture ±30 min. Previous publications (10) have shown that there may be both decreases and increases in plasma cortisol levels between 8.30 and 11.00 a.m. After 11.00

Table 3

Product–moment correlations between psychiatric and endocrinologic parameters (means and linear time trends) during the study periods preceding death. (In these analyses at least two observations were required before death)

	Depression		Anxiety		Mental exhaustion	
	Mean	Linear time trend	Mean	Linear time trend	Mean	Linear time trend
Cortisol						
r	−0.14	0.17	−0.17	−0.04	−0.17	0.29*
n	64	59	64	57	62	56
Log prolactin						
r	−0.21**	0.10	−0.15	−0.04	−0.16	−0.28*
n	62	55	62	53	64	52

* $p<0.05$
** $p<0.10$

a.m., however, we expected a fall of cortisol levels to the late afternoon. We decided to divide the subjects in both groups into 3 subgroups with regard to time of venipuncture, corresponding to the time intervals 8.30 to 11.00 a.m. 11.00 a.m. to 2.00 p.m. and 2.00 to 4.00 p.m. The mean cortisol levels in these 3 subgroups in the combined population at the last observation before the patient's death were 486, 426 and 409 nmol/l (non significant by analysis of variance). For prolactin no obvious circadian rhythm was observed at all. In order to adjust for differences in time of day the period of venipuncture (8.30–11.00 a.m., 11.00 a.m. to 2.00 p.m. and 2.00–4.00 p.m.). was used as covariate (10). All blood tests were taken in sitting position at the hospital without previous rest. The plasma was separated from each blood sample, frozen and stored at −20°C. Both cortisol (3) and prolactin (4) were determined by radioimmuno assay. In the statistical analyses logarithms of the concentrations were used since the distribution of prolactin levels is markedly skewed.

Statistical Methods

Since the endocrinological variables and the psychiatric scores were approximately normally distributed, statistical tests were carried out in order to investigate any significant differences between the comparison and the activation group, both during the period of patient's disease and after death.

Variations within subjects as well as between groups were studied. In the 'within subjects' analyses, paired t-tests were used in the follow-up of endocrinological changes after death. In this case, changes in prolactin and cortisol levels were calculated from the last observation preceding the patient's death to one and two months after, and the statistical significance of the change was computed for the activation group as well as for the comparison one. In the other 'within-subject' tests, analyses of variance were used. In this case the statistical significance of changes in the total study group (activation and comparison) is estimated. The 'between group' differences were studied by means of two-tailed t-tests for uncorrelated means as well as by means of analyses of variance. Finally, the analyses of the 'within subjects' and 'between groups' differences were combined by means of a two-way analysis of variance. All the statistical analyses of hormone levels before-after the patients died were performed on women who had complete data for all these occasions. Furthermore, two groups of correlations based on the total study group (activation and comparison) were computed:

1) Product–moment correlations between mean levels of psychiatric and endocrinological parameters during the treatment period.

2) Product–moment correlations between time trends in psychiatric and endocrinological parameters. The time trends were computed by means of linear regression analysis. Thus, the number of observation was used as the independent and the endocrinological or psychiatric variable as the dependent variable. This computation was performed for each variable and the regression coefficient was used as a measure of the time trend.

Results

Table 3 shows the results of the correlation analysis including women in both programmes.

Prolactin levels in general tended to be ($p=0.08$) lower in women who showed clear evidence of depression ($r=-0.21$). Anxiety showed no correlations to the endocrine parameters. For mental exhaustion, the linear trends were correlated both to cortisol and prolactin levels. When the degree of mental exhaustion increased during the treatment period the cortisol levels tended to increase ($r=0.29$, $p<0.05$) and the prolactin levels to decrease ($r=-0.28$, $p<0.05$).

Table 4

Two-way analysis of variance for observations of endocrinologic parameters before, one month after and two months after death of patient. Activation and comparison groups (only relatives of patients who died). Means adjusted with regard to time of day. (F, group=analysis of variance with regard to inter-group differences, F, time=analysis of variance with regard to the effect of time (within subjects) and F. interaction = analysis with regard to the interactive effect of time and group on endocrine level ('mixed model' analysis)

	Cortisol		Prolactin*	
	Activation** (n=14)	Comparison*** (n=11)	Activation** (n=13)	Comparison*** (n=11)
Before	619±78	437±59	0.92±0.04	0.96±0.07
1 month after	492±66	391±50	0.90±0.06	0.90±0.06
2 months after	510±72	412±44	0.91±0.05	0.85±0.05
F, group	=1.97	p=0.17	F=0.01	p=0.92
F, time	=3.24	p=0.05	F=0.75	p=0.48
F, interaction	=0.91	p=0.41	F=0.53	p=0.59

* One subject lost due to insufficient amount of blood.
** Paired two-tailed t-tests were performed in order to determine if there was any statistically significant difference in mean level measured at the last observation before death on one hand and mean levels measured 1 and 2 months respectively after death on the other hand.
Before—1 month after death: $t = 3.20$ ($p<0.01$)
Before—2 months after death: $t = 2.29$ ($p<0.05$)
*** The corresponding tests for the comparison group were non-significant.

Table 4 shows the prolactin and cortisol results of the two-way analysis of variance for the activation and comparison groups, observations preceding the patient's death and one and two months after death.

The cortisol levels were very high immediately before the death of the patient in the activation group. Significantly decreased levels were seen in the activation group one month after the death of the patient compared with those at the last observation before the patient's death ($p<0.01$). No statistically significant differences or trends were observed.

The Figure 1 a) shows the cortisol levels and b) the prolactin plasma levels in relatives in relation to the course of the patient's illness in the activation and comparison groups during the treatment period and the terminal stage as well as 1 month and 2 months after the death of the patient. During the treatment period the prolactin levels tended to be lower in the activation group ($p<0.06$).

During the treatment period, there were no significant differences between the groups with regard to mean psychiatric scores.

The results of the t-test analysis for the last observation preceding death (the scores are not strictly comparable to those obtained after death) showed that exhaustion scores were significantly lower in the activation group than in the comparison group ($p<0.05$). (10.0±0.2 vs 10.8±0.3, $t=2.07$)

The results of the two-way analysis of variance one and two months after the death of the patient showed that significant improvement occurred from one to two months after death for all the psychiatric scores. For mental exhaustion, the scores were significantly lower in the activation group than in the comparison group ($p<0.01$) (after 1 month 9.6±0.3 and 10.9±0.4 and after 2 months 8.8±0.3 and 10.1±0.4 respectively).

Table 5

Summary of the findings in the activation group vs. comparison group

	Endocrinological	Psychiatric
Average level during treatment period	Depressed prolactin	No difference
Last observation before death of patient	Elevated cortisol	Lowered exhaustion score
1 and 2 months after death	No difference	Lowered mental exhaustion score Scores decreasing from one to two months after death in both groups

Table 5 gives a summary of the endocrinological and psychiatric findings in the activation group versus the comparison group during the treatment period, at the last observation before death of the patient and at 1 and 2 months after death.

Discussion

One interpretation of the results is that female relatives of cancer patients, after having been stimulated to take

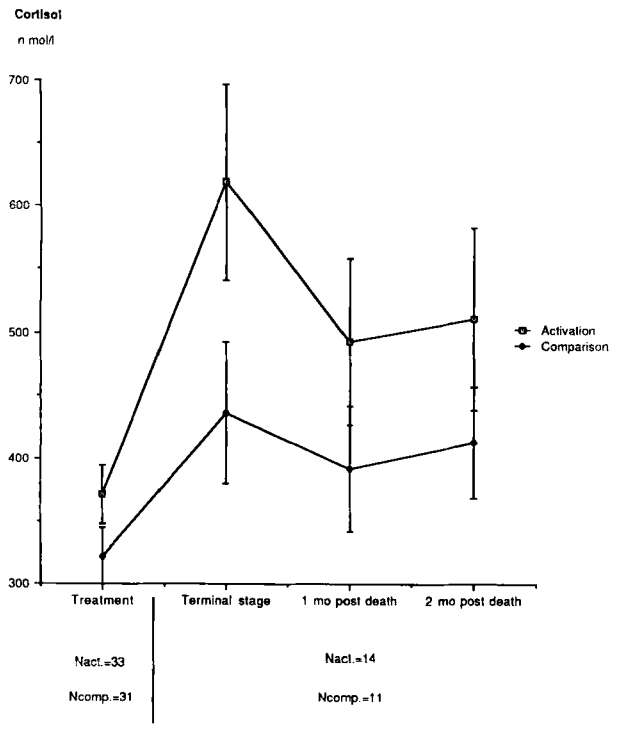

Fig. 1a. Means and standard errors of means of cortisol levels in relatives in relation to the course of the patient's illness in the activation and comparison conditions.

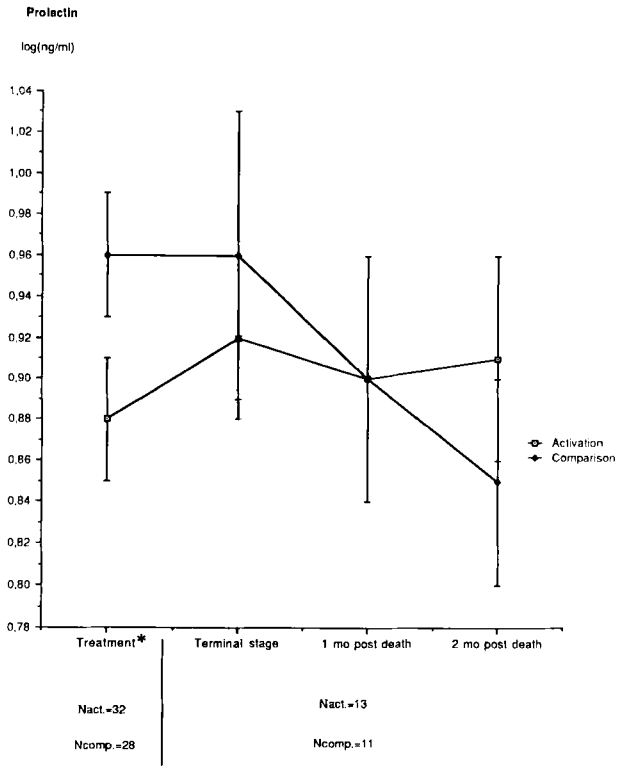

Fig. 1b. Means and standard errors of means of prolactin levels in relatives in relation to the course of the patient's illness in the activation and comparison conditions.
* Two tailed t-tests for uncorrelated means during treatment period $p=0.06$.

more active part in the care of the patient than is the case in usual wards, have a depressed serum prolactin level during the treatment period. During the terminal care period, when the patient is soon going to die, women in this group react with elevated serum cortisol levels but also with decreased mental exhaustion compared with women in the comparison group. After the death of the patient, women who were offered more active participation in the care of the patients also showed less evidence of psychological exhaustion.

Possible sources of error were discovered. Each woman had all blood samples drawn at a constant hour of the day, but the blood samples were not always drawn in the early morning—more women in the comparison group than in the activation group had their blood tests drawn in the morning. This source of error was treated by means of statistical covariance—after correction for time of day the differences between the groups were statistically significant. Another source of error could be seasonal variation since serum prolactin levels tend to be higher during the summer months than during the winter period (1) and more women in the comparison group than in the activation one were examined partly during the summer months. This was not observed to make any difference —the average log (serum prolactin level) among women in the activation group studied partly during the summer months was 0.88 and the corresponding average level in the comparison group 0.96. Among women who were examined during the winter months the corresponding mean levels were 0.87 (activation) and 0.96 (comparison). Thus the differences were unaffected by season. It is likely that the dramatic crisis reaction occurring when a close relative is treated for cancer overrides the importance of seasonal variation.

The findings in the literature regarding prolactin levels in relation to psychological processes are difficult to interpret. In general previously reported findings are in agreement with our findings, i.e. that increasing levels of psychological exhaustion in one and the same individual are associated with decreasing levels of prolactin. Some authors have reported elevated and others lowered prolactin levels during psychiatric depression (8). It is likely that the time of day as well as the stage of psychiatric reaction may be of importance. In the present study, the prolactin levels were studied from the morning until the early afternoon. The depressed prolactin levels were only observed during the early stages of the psychiatric grief process, not after the death of the patient. In general, psychiatric disturbances are known inhibitors of the lactation (5), and this is in line with the present finding that women more actively involved in the grief process have a lowered prolactin level.

The findings regarding serum cortisol are in agreement with previously reported findings. Periods of intense psychiatric depression have been reported to be associated with elevated serum cortisol levels (9). Plasma cortisol levels have not shown significant seasonal variation in previous studies (1). Therefore, for cortisol the difference in months of examination was judged to be unimportant. If anything, this source of error would tend to bias the results against the observed difference.

It should be pointed out that all relatives to patients, cared for in the ward during the activation programme period, were regarded as 'activated'. Thus, we have not taken account of the fact that several relatives did not accept the offer to participate more actively in the care. We have followed this principle in order to avoid 'selection effects', i.e. false positive effects. It could otherwise be the case that those who are initially the most healthy and the most socially active recover most rapidly psychologically and also participate most actively in the programme without the programme and the recovery being related. As a result of the use of the intention-to-treat principle the demonstrated treatment effect was probably less than the true effect. Furthermore, the plans for the activation programme in the activation ward were known in the whole department. Therefore the personnel in the comparison wards may have been more active in their communication with relatives than normally. This may also have tended to reduce the differences.

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