

CLINICAL STUDY

Life events in the pathogenesis of hyperprolactinemia

N Sonino, C Navarrini², C Ruini², F Fallo¹, M Boscaro³ and G A Fava²

Departments of Statistical Sciences and Department of Mental Health and ¹Department of Medical and Surgical Sciences, University of Padova, Padova, Italy, ²Department of Psychology, University of Bologna, Bologna, Italy and ³Division of Endocrinology, University of Ancona, Ancona, Italy

(Correspondence should be addressed to N Sonino, Department of Statistical Sciences, University of Padova, Via Battisti 241, 35121 Padova, Italy; Email: nicoletta.sonino@unipd.it)

Abstract

Objective: Little is known about the relationship between recent life events and onset of hyperprolactinemia, despite the well-known effect of acute psychological stress on prolactin levels in healthy subjects. Recent life events in patients with hyperprolactinemia compared with healthy controls were investigated.

Design: Case–control study.

Methods: Fifty-two consecutive patients with hyperprolactinemia (45 females/7 males; mean age 34.9 ± 10.1 years, range 18–60 years) and 52 healthy subjects matched for socio-demographic variables were studied. Nineteen patients (18 females/1 male) had no pituitary tumor and were diagnosed as suffering from idiopathic hyperprolactinemia. Patients with additional pathology or with high prolactin due to medications were excluded. All patients were interviewed by Paykel Interview for Recent Life Events while on remission after surgery or pharmacological treatment. The time period considered was the year preceding the first signs of hyperprolactinemia, and the year before interview for controls.

Results: Patients with hyperprolactinemia reported significantly more life events than control subjects ($P < 0.001$). The same significant difference compared with controls applied to patients with ($n = 16$) and without ($n = 36$) depression. All categories of events (except events that were likely to be under the subject's control) were significantly more frequent. There were no significant differences between patients with prolactinoma ($n = 33$) and those with idiopathic hyperprolactinemia ($n = 19$).

Conclusions: Within the complexity of phenomena implicated in the pathogenesis of hyperprolactinemia, our findings emphasize a potential role of emotional stress in either prolactin-secreting pituitary tumors or idiopathic hyperprolactinemia. Appraisal of life stress may have implications in clinical assessment (e.g. functional hyperprolactinemia) and decisions (e.g. termination of long-term pharmacological treatment).

European Journal of Endocrinology 151 61–65

Introduction

Several investigations have suggested a role for stressful life events in uncovering a person's vulnerability to an endocrine disorder (1). By 'life events' we mean discrete changes in the subject's social or personal environment, that should be external and verifiable rather than internal or psychological. The use of structured methods of data collection has indicated that stressful life events were significantly more frequent in Cushing's disease (2) and Graves' disease (3–6) compared with control groups.

Little is known about the relationship between recent life events and onset of hyperprolactinemia, despite the well-known relationship between acute psychological stress and prolactin levels in healthy subjects (7, 8). Nunes *et al.* (9) observed that menstrual abnormalities, galactorrhea and other symptoms of hyperprolactinemia often had an acute onset in close

temporal association with important events in the patient's life, such as marriage or actual or threatened loss of an important person. Assies *et al.* (10), in a small controlled study, failed to detect significant differences between hyperprolactinemic patients and controls in stressful life experiences. Both studies (9, 10), however, did not use standardized methods of life event assessment.

More extensive evidence is available on the role of early life situations. The biographic and clinical investigation of 101 patients with hyperprolactinemia and/or galactorrhea by Nunes *et al.* (9) suggested that exposure during childhood to an environment characterized by an absent or alcoholic, violent father may condition some women to develop hyperprolactinemia and/or galactorrhea later in life as a response to specific environmental changes. These observations were confirmed when sisters of patients with prolactinoma (generally exposed to the same environment as the patients)

and a control group were studied (11). Higher mean serum prolactin concentrations and higher incidence of hyperprolactinemia and galactorrhea were found in women with paternal deprivation during childhood. In another investigation (10), significantly more separations during childhood were reported. Finally, patients with hyperprolactinemic amenorrhoea were found to have had functional enuresis during childhood significantly more frequently than women with amenorrhoea and normal prolactin levels (12).

The aim of this study was to provide a controlled evaluation of recent life events in patients with hyperprolactinemia compared with healthy control subjects matched for socio-demographic variables, using methods (13) that have been found to be valid and reliable in other investigations concerned with endocrine disorders (2, 4, 6).

Subjects and methods

Subjects

This study involved 52 consecutive patients with hyperprolactinemia, who had an established diagnosis and treatment, and a control group of 52 healthy subjects matched for age (in decades), sex, marital status and social class. The mean age (\pm s.d.) was 34.9 ± 10.1 years (range 18–60 years). There were 45 females and 7 males: 30 were married; 28 belonged to the working class and 24 to the middle-upper class according to Goldthorpe and Hope's occupational classification (14).

The initial diagnosis was based on clinical features and high prolactin levels: 242.6 ± 521.0 ng/ml (mean \pm s.d.). Morphological assessment included magnetic resonance imaging in all patients. Thirty-three patients (27 females and 6 males; mean age 34.4 ± 10.6 years, age range 18–60 years; mean prolactin levels 347.7 ± 633.2 ng/ml) had a prolactin-secreting pituitary tumor (microprolactinoma in 27 and macroprolactinoma in 6). Nineteen patients (18 females and 1 male; mean age 35.7 ± 9.5 years, age range 23–53 years; mean prolactin levels 60.1 ± 32.1 ng/ml) were not found to have a pituitary tumor and were diagnosed as suffering from idiopathic hyperprolactinemia. Patients with additional pituitary abnormalities and/or additional pathology (15) were excluded, as were those with hyperprolactinemia due to medication.

All patients were interviewed while on remission after surgery or pharmacological treatment with dopamine agonists (16–18) and therefore not in the hyperprolactinemic state. Informed consent was obtained in all cases.

Methods

Paykel's Interview for Recent Life Events (13) covering 64 life events was administered as a semistructured

research interview. The time period for which events were recorded was the year preceding the first symptoms of hyperprolactinemia, as assessed by an experienced endocrinologist, and the year before the interview for control subjects. All patients and controls were seen by the same interviewer. Detailed questioning was carried out by a clinical psychologist to determine the full nature and circumstances of each event reported. Two ratings were carried out by an independent blind rater, who was unaware whether the event had occurred in a patient or a control subject: (1) the objective negative impact (contextual threat), i.e. the rater makes judgment of the expected stressfulness of the event, when its full nature and particular circumstances are taken into account, ignoring the subjective reaction of the patient; (2) independence (the likelihood that the event is not a consequence of illness). The presence of a major depressive disorder, according to the American Psychiatric Association's *Diagnostic and Statistical Manual* DSM-IV criteria (19) was assessed with a semistructured research interview (20) by the same interviewer.

Prolactin was measured by immunoradiometric assay (IRMA) by a commercial kit (BioChem Immuno-Systems, Bologna, Italy). Intra-assay and interassay coefficients of variations were both $< 7\%$. Normal values were 2.6–26 ng/ml in women and 2.0–14.5 ng/ml in men.

Statistical analysis

Results are expressed as means \pm s.d. Comparisons between patients and controls were carried out by the two tailed *t*-test and the χ^2 test, as appropriate; *P* values < 0.05 were considered to be significant.

Results

Patients with hyperprolactinemia reported significantly more life events than control subjects (Table 1). When only events 'almost certainly independent' or 'probably independent' of illness (events not caused by the illness or its psychiatric consequences) were considered and those that were rated as 'uncertain', 'probably dependent' or 'almost certainly dependent' were excluded, patients still reported significantly more events than

Table 1 Number of life events in patients with hyperprolactinemia ($n = 52$) compared with controls ($n = 52$).

	Patients (mean \pm s.d.)	Controls (mean \pm s.d.)	<i>t</i> (d.f. = 102)	<i>P</i>
Total number	3.42 ± 1.58	0.56 ± 0.64	12.15	< 0.001
Independent	2.97 ± 1.58	0.44 ± 0.64	10.23	< 0.001
Negative impact	2.42 ± 1.47	0.10 ± 0.30	11.16	< 0.001

Table 2 Categories of life events in patients with hyperprolactinemia ($n = 52$) compared with controls ($n = 52$). Number of individuals reporting at least one event in any category.

Category	Patients	Controls	χ^2 (d.f. = 1)	<i>P</i>
Entrances	25	10	8.44	<0.01
Exits	35	7	29.11	<0.001
Desirable events	24	9	8.34	<0.01
Undesirable events	48	16	39.04	<0.001
Controlled events	16	14	0.05	NS
Uncontrolled events	45	6	55.56	<0.001

controls (Table 1). A further comparison was made of the objective negative impact of the events. Again, patients with hyperprolactinemia reported significantly more events rated as being of moderate, marked or severe negative impact compared with controls (Table 1).

Table 2 displays three categories of events (13): (1) entrances (involving introduction of new people, such as marriage) and exits (involving departure of a person from the social field of the subject, such as the death of a close family member); (2) either socially desirable (e.g. promotion) or undesirable (e.g. major financial problems) events; (3) controlled events (when the initiation of the event was likely to be under the subject's control or choice) or uncontrolled events (not likely to be under control or against one's wish). All categories of events, except controlled events, were found to be significantly more frequent in patients suffering from hyperprolactinemia than in controls.

All analyses were repeated separating patients with idiopathic hyperprolactinemia ($n = 19$) from those with prolactinomas ($n = 33$). Since they yielded similar results, the analyses are not reported here.

Sixteen patients (30.8%) were identified as suffering from a major depressive disorder according to DSM-IV criteria (19). The sample was therefore analyzed separating patients with depression from those without. There were significant differences in life events compared with controls for both depressed ($P < 0.001$) and non-depressed ($P < 0.001$) patients.

Discussion

In patients with hyperprolactinemia, life events were significantly more frequent than in control subjects and rather heterogeneous in quality: at times they involved positive and desirable changes (increasing, however, the challenge for the individual); at other times they were undesirable, uncontrolled and with objective negative impact. Several studies involving real-life stress in non-clinical populations suggest that change situations associated with passive coping

appear to be accompanied by increased plasma prolactin levels, whereas change situations associated with active coping do not seem to affect prolactin (21). Indeed, in our investigation, the excess in life stress involved uncontrolled, but not controlled, events. As to categories of events, previous research (in psychiatric patients) using Paykel's interview (13) had linked losses, and undesirable and uncontrolled events to major depression and Cushing's disease (2). Instead, the heterogeneous pattern found in hyperprolactinemia was more typical of anxiety disturbances (22) and Graves' disease (4). This is also consistent with the high prevalence of anxiety disturbances in hyperprolactinemia (23, 24), including those patients in remission (25–27).

Retrospective studies have obvious inherent risks. One can argue that an excess of life events in patients with hyperprolactinemia compared with controls may be the consequence rather than the cause of illness. Events such as marital separation, even if they occurred before any clear sign of the disorder, may have been caused by its insidious development. For instance, anxiety and irritability resulting from hyperprolactinemia (23) could lead to interpersonal friction, and thus to separation. However, when the events potentially dependent on illness were excluded, there were still highly significant differences between patients and controls. Further, the ratings concerned with independence and objective negative impact were performed by a blind rater. One can also argue that patients with hyperprolactinemia do not actually experience more events prior to illness, but simply recall more of them, or that they selectively remember more upsetting events (28). If the patient or his relatives are questioned about events during the acute phase of illness, they tend to distort their meaning and magnitude, whereas when patients improve they tend to minimize the reporting of negative events (29). Accordingly, patients with hyperprolactinemia were not interviewed during the acute phase of illness, but upon remission, when affective symptoms tend to subside (24). Another source of error in retrospective studies is distortion of recall: the more distant the period of recall, the more likely is the life change to be underestimated and the accuracy of recall to be inversely proportional to the remoteness of the time period being recalled (30). While control subjects were questioned about events occurring in the year preceding the interview, the time period for patients with hyperprolactinemia was variable, due to different times of disease onset. However, unlike self-rating scales, observer-rated instruments are designed to facilitate temporal organization of personal facts (31). Paykel's interview has very high test–retest reliability (that is good concordance about the reporting of events by a subject concerning a specific period and the subsequent questioning of the subject at some later point in time about the same period), inter-rater reliability (there is agreement

between two raters as to the occurrence of a specific event on 95% of occasions) and concordance between the information provided by the subject and that obtained from other sources (usually a relative) (13, 32).

In view of the methods used (careful dating of the onset of symptoms, rigorous event definition, delay of the interview until hormone abnormalities are corrected, use of a blind rater for judging independence and objective negative impact), the results suggest a role for life events in the pathogenesis of hyperprolactinemia. There is evidence that several factors may contribute to the occurrence of hyperprolactinemia (15, 16). In prolactinomas, stress might facilitate clonal proliferation of a single mutated cell. In functional hyperprolactinemic states, stress in predisposed individuals (24) might trigger neuroendocrine changes involving dopamine and/or serotonin, which affect prolactin release (33). The retrospective nature of our investigation and the slow pathophysiological process of hyperprolactinemia (potentially extending over years) do not allow us to ascertain whether stressful life events may be related to the onset of illness or its manifestations (symptom formation). Nonetheless, within the complexity of phenomena implicated in the pathogenesis of hyperprolactinemia (15, 16), our findings emphasize a potential role of emotional stress. The findings lend support to the studies suggesting a high prevalence of psychological distress in hyperprolactinemia (23–27) and may alert physicians to enquire about the relevance of stress in the patient's life. Appraisal of the psycho-social dimension may have important practical implications in the handling of each individual patient and in the theoretical configuration of the pathogenesis of hyperprolactinemic disorders.

Acknowledgements

This study was supported in part by a grant from the Consiglio Nazionale delle Ricerche (CNR, Roma, Italy) to N S and grants from Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, Roma, Italy) to N S and G F.

References

- Sonino N & Fava GA. Psychological aspects of endocrine disease. *Clinical Endocrinology* 1998 **49** 1–7.
- Sonino N, Fava GA & Boscaro M. A role for life events in the pathogenesis of Cushing's disease. *Clinical Endocrinology* 1993 **38** 261–264.
- Winsa B, Adami HO, Bergstrom B, Gamstedt A, Dahlberg PA, Adamson U, Jansson R & Karlsson A. Stressful life events and Graves' disease. *Lancet* 1991 **338** 1475–1479.
- Sonino N, Girelli ME, Boscaro M, Fallo F, Busnardo B & Fava GA. Life events in the pathogenesis of Graves' disease. *Acta Endocrinologica* 1993 **128** 293–296.
- Kung AWC. Life events, daily stresses and coping in patients with Graves' disease. *Clinical Endocrinology* 1995 **45** 715–720.
- Radosavljevic VR, Jakovic SM & Marinkovic JM. Stressful life events in the pathogenesis of Graves' disease. *European Journal of Endocrinology* 1996 **134** 699–701.
- Fava M & Guaraldi GP. Prolactin and stress. *Stress Medicine* 1987 **3** 211–216.
- Biondi M & Picardi A. Psychological stress and neuroendocrine function in humans. *Psychotherapy and Psychosomatics* 1999 **68** 114–150.
- Nunes MCP, Sobrinho L, Calhaz-Jorge C, Santos MA, Mauricio JC & Sousa MFF. Psychosomatic factors in patients with hyperprolactinemia and/or galactorrhea. *Obstetrics and Gynecology* 1980 **55** 591–595.
- Assies J, Vingerhoets AJJM & Poppelaars K. Psychosocial aspects of hyperprolactinemia. *Psychoneuroendocrinology* 1992 **17** 673–679.
- Sobrinho LG, Nunes MCP, Calhaz-Jorge C, Afonso AM, Pereira MC & Santos MA. Hyperprolactinemia in women with paternal deprivation during childhood. *Obstetrics and Gynecology* 1984 **64** 465–468.
- Fava M, Guaraldi GP, Borofsky GL & Mastrogiacono I. Childhood enuresis in the history of women with hyperprolactinemic amenorrhea. *International Journal of Psychiatry in Medicine* 1989 **19** 41–46.
- Paykel ES. The Interview for Recent Life Events. *Psychological Medicine* 1997 **27** 301–310.
- Goldthorpe JH & Hope K. *The Social Grading of Occupations*. Oxford: Oxford University Press, 1974.
- Molitch ME. Disorders of prolactin secretion. *Endocrinology and Metabolism Clinics of North America* 2001 **30** 585–610.
- Verhelst J & Abs R. Hyperprolactinemia. Pathophysiology and management. *Treatments in Endocrinology* 2003 **2** 23–32.
- Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R & Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and non tumoral hyperprolactinemia. *New England Journal of Medicine* 2003 **349** 2023–2033.
- Schlechte JA. Prolactinoma. *New England Journal of Medicine* 2003 **349** 2035–2041.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. (DSM-IV). Washington, DC: American Psychiatric Association, 1994.
- Paykel ES. The Clinical Interview for Depression. *Journal of Affective Disorders* 1985 **9** 85–96.
- Theorell T. Prolactin. A hormone that mirrors passiveness in crisis situations. *Integrative Physiology and Behavioral Sciences* 1992 **27** 32–38.
- Barrett JE. The relationship of life events to the onset of neurotic disorders. In *Stress and Mental Disorder*, pp 87–109. Ed JE Barrett. New York: Raven Press, 1979.
- Fava GA, Fava M, Kellner R, Serafini E & Mastrogiacono I. Depression, hostility and anxiety in hyperprolactinemic amenorrhea. *Psychotherapy and Psychosomatics* 1981 **36** 122–128.
- Sobrinho LG. Emotional aspects of hyperprolactinemia. *Psychotherapy and Psychosomatics* 1998 **67** 133–139.
- Reavley S, Fisher AD, Owen D, Creed FH & Davis JRE. Psychosocial distress in patients with hyperprolactinemia. *Clinical Endocrinology* 1997 **47** 343–348.
- Sonino N, Navarrini C, Ruini C, Ottolini F, Paoletta A, Fallo F, Boscaro M & Fava GA. Persistent psychological distress in patients treated for endocrine disease. *Psychotherapy and Psychosomatics* 2004 **73** 78–83.
- Sobrinho L. Psychopathology in endocrine disorders: why so persistent after the cure? *Psychotherapy and Psychosomatics* 2004 **73** 65–67.
- Brown GW & Harris T. Establishing causal links. In *Life Events and Psychiatric Disorder*, pp 107–187. Ed H Katsching. Cambridge: Cambridge University Press, 1986.
- Fava GA & Kellner R. Prodromal symptoms in affective disorders. *American Journal of Psychiatry* 1991 **148** 823–830.

- 30 Hurst MW. Life changes and psychiatric symptom development. In *Stress and Mental Disorder*, pp 17–36. Ed JE Barrett. New York: Raven Press, 1979.
- 31 Bradburn NM, Rips LJ & Shevell SK. Answering autobiographical questions. *Science* 1987 **236** 157–161.
- 32 Baratta S, Colorio C & Zimmermann-Tansella Ch. Inter-rater reliability of the Italian version of the Paykel Scale for stressful life events. *Journal of Affective Disorders* 1985 **8** 279–282.
- 33 Freeman ME, Kanyicska B, Lerant A & Nagy G. Prolactin: structure, function, and regulation of secretion. *Physiological Reviews* 2000 **80** 1523–1631.
-

Received 4 February 2004

Accepted 25 March 2004