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Steroid induced Psychiatric Syndromes in Patients with Chronic Glomerulonephritis

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Abstract

Background. The occurrence of psychiatric symptoms in association with the clinical use of corticosteroids has been documented since the introduction of steroids as therapeutic agents over 50 years ago. There are some studies in the literature which address limited aspects of this problem, but there are no adequately controlled comprehensive studies of the psychiatric effects of steroid therapy in patients with chronic glomerulonephritis.
Methods. We reviewed case records at the Clinic of Internal Disease and Therapy and Clinic of Rheumatology, previous case reports and other sources of information in the literature in order to improve our understanding of these disorders.
Results. Our findings indicate that severe psychiatric reactions occur in approximately 2% of steroid-treated patients, and the large proportion of these patients have affective and/or psychotic symptoms. None of our patients had a past history of psychiatric illness unrelated to steroid therapy. Psychiatric disturbances usually occur early in the course of steroid therapy (1 to 76 days). Female sex, systemic lupus erythematosus and high doses of prednisolone (only two of the patients with significant psychiatric syndromes had been receiving less than 40 mg/24 h of prednisolone before the onset of symptoms) may be risk factors for development of the steroid-induced psychiatric syndrome. The duration of symptoms ranged from 2 to 48 days, with a mean of 18 days, irrespectively of the treatment. 20 of our cases had a complete recovery from their steroid-induced psychiatric syndrome.
Conclusion. Patients with delirium have a significantly shorter duration of symptoms than patients who developed an affective syndrome. Treatment with steroid-taper, neuroleptics or electroconvulsive therapy with regard to the clinical status is generally effective in these patients.

Keywords: adverse psychiatric effects, corticosteroids, chronic glomerulonephritis

Introduction

Although it is well-established that psychiatric symptoms can develop in association with the administration of corticosteroids, the nature of this relationship is poorly understood. Early reports consisted of detailed description of individual cases [1,2] and these observations and conclusions have sometimes been uncritically reproduced in the reviews of the literature. Sometimes, others have cited the options reported in the previous reviews, which in turn based their conclusions on the clinical observations of the early authors [3]. On the other hand, a few authors were intrigued whether corticosteroids cause psychiatric adverse effects at all [3, 4]. A recent meta-analysis of randomized controlled trials has provided a firm confirmation that it is quite possible [5]. The association of corticosteroid treatment with depressive and manic syndromes is relatively well documented, although, there is a need for additional prospective studies in various clinical populations and settings under the use of corticosteroids. Thus, the frequency and severity of these disturbances within specific populations can be more clearly elucidated. A search in the Medline and psycINFO databases (conducted to find clinically relevant articles on psychiatric side effects from corticosteroids) with search terms like glomerulonephritis, corticosteroid, prednisone, mania, depression, and psychosis occuring during corticosteroid therapy ascertain the fact that there are only a few published articles about psychiatric side effects of corticosteroids in patients with glomerulonephritis.
In an attempt to find additional information about the incidence and other aspects of steroid-induced psychiatric syndromes, we studied the adverse effects of corticosteroids in the patients with chronic glomerulonephritis.

Patients and methods

Review of the case records (365) at the Clinic of Internal Disease and Therapy and Clinic of Rheumatology from 1985 through 2005 revealed 21 cases of psychiatric syndromes. 7 of them ($P<0.05$) in patients with biopsy proven glomerulonephritis, were associated with the administration of steroid therapy. From a review of the case notes and the consulting psychiatrist's evaluation we were able to obtain the following information about each patient: age, sex, history of previous psychiatric illness, premorbid adjustment and personality characteristics, medical indication for steroid treatment, dose and duration of steroid treatment, history of other courses of steroid therapy. These 21 patients fulfilled the following criteria: a) no previous psychiatric history and b) DSM-IV (Diagnostic and statistical Manual of Mental Disorders, 4th edition) criteria [6] for corticosteroid-induced psychotic or mood disorder. By reviewing notes and evaluations of these cases by consultant psychiatrists, we aimed to elucidate the clinical

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characteristics including the psychiatric symptomatology, response to the treatment and the outcome.

The following statistical methods were applied: parametric Student's t-test and Fisher's exact test for nominal variables, correlation analysis (daily dose/type of syndromes; age/development of steroid-induced psychiatric syndromes and others) and variation analysis to determine the independent factors related with psychiatric syndromes. Continuous data are presented as mean (±SD) and categorical data as number (percentage). For all analyses p values less than or equal to 0,05 were considered statistically significant.

Results

We studied 356 patients (195 female, 161 male; mean age 45,7±9,6 years) with glomerulonephritis (207 of them with lupus glomerulonephritis) without previous history of psychiatric illness unrelated to steroid therapy (Table 1).

Oral prednisolone was the most frequently (354 patients) administered therapy. Intravenous methylprednisolone was given to 287 patients for corticosteroid pulse therapy at a dose of 500 mg or 1g/24 h for 3 consecutive days. Our findings indicate that psychiatric reactions (7 - severe psychiatric reactions and 14 - mild isolated psychiatric syndromes) occur in 21 of steroid-treated patients with glomerulonephritis (20 female, 1 male; mean age 34,1±6,2 years), and all being with affective and/or psychotic symptoms (Table 2). Corticosteroids can provoke both mania (6 patients – 28,57%) and depression that clinically appear opposite to each other. Underlying medical disease in 14 of these patients was Systemic lupus erythematosus (mesangial proliferative lupus nephritis – 5 patients, focal lupus nephritis – 1 patient, diffuse lupus nephritis – 6 patients, membranous lupus nephritis – 2 patients). The presence and severity of individual symptoms varied during the course of the illness. Depression (8 patients - 38,1%) is the most common psychiatric disturbance. Two (9,52 %) of the patients had delirium characterized by a clouding of consciousness, disorientation, changes in psychomotor activity and rapid fluctuations in symptoms. Five (23,81 %) of the cases suffered from a psychotic disorder without evidence of a significant mood change or features of a delirium.

Table 1. Biopsy parameters in patients with chronic glomerulonephritis

Characteristics	
Female gender	**195**
Age (years)	**45,7 ± 9,6**
Biopsy parameters in patients with lupus nephritis	**N of patients**
Minimal mesangial lupus nephritis	**16**
Mesangial proliferative lupus nephritis	**28**
Focal lupus nephritis	**17**
Diffuse lupus nephritis	**99**
Membranous lupus nephritis	**47**
Activity index	**9,5 ± 2,3**
Chronicity index	**2,4 ± 1,7**
Biopsy parameters in patients with chronic glomerulonephritis [non-lupus]	
Minimal change nephropathy	**11**
Focal segmental glomerulosclerosis	**8**
Mesangiocapillary glomerulonephritis	**5**
Mesangial proliferative (IgA) glomerulonephritis	**25**
Diffuse proliferative glomerulonephritis	**58**
Membranous nephropathy	**42**

Table 2. Distribution of types of steroid-induced psychiatric syndromes

PSYCHIATRIC SYNDROME	TOTAL (%)	TYPE OF CHRONIC GLOMERULONEPHRITIS
Depression	8 (38,1 %)	SLE. Mesangial proliferative lupus nephritis - 2 patients
		SLE. Diffuse lupus nephritis – 2 patients
		Diffuse proliferative glomerulonephritis (non-lupus) - 3 patients
		Membranous nephropathy – 1 patient
Mania	6 (28,57 %)	SLE. Mesangial proliferative lupus nephritis - 1 patient
		SLE. Diffuse lupus nephritis – 1 patient
		SLE. Focal lupus nephritis – 1 patient
		SLE. Membranous lupus nephritis - 1 patient
		Mesangiocapillary glomerulonephritis (non-lupus) - 2 patients
Psychosis	5 (23,81 %)	SLE. Mesangial proliferative lupus nephritis -1 patient
		SLE. Diffuse lupus nephritis – 2 patients
		SLE. Membranous lupus nephritis - 1 patient
		Diffuse proliferative glomerulonephritis (non-lupus) - 1 patients
Delirium	2 (9,52 %)	SLE. Diffuse lupus nephritis – 1 patient
		SLE. Mesangial proliferative lupus nephritis – 1 patient

The duration of treatment with steroids before the onset of psychiatric symptoms ranged from 1 to 76 days. 33,33 % of the cases developed symptoms during the first week of treatment, 71,43 % - within the first 2 weeks, and 95,24 % - within 6 weeks of the initiation of steroid therapy. Only two patients with significant psychiatric syndromes received less than 40 mg/24 h of prednisolone before the onset of symptoms.

The duration of symptoms ranged from 2 to 48 days, with a mean of 18 days, irrespective of treatment. 20 of our cases had a complete recovery from their steroid-induced psychiatric syndrome. Patients with a delirium have a significantly shorter duration of symptoms than do patients who develop an affective syndrome. There were no statistically significant differences in duration of symptoms among the depressive, manic or psychotic groups.

Treatment with steroid-taper, neuroleptics or electroconvulsive therapy, based on the clinical picture, was generally effective in these patients. Despite the small number of subjects in this study, we could not observe recurrences unrelated to corticosteroid treatment in psychotic disorder patients.

Discussion

Corticosteroids can affect various psychiatric functions, including mood, cognition, and thought, and can induce different psychiatric syndromes based on the patient's vulnerability. Changes in mood or affect, such as mild euphoria or depression are the most frequently seen psychiatric symptoms [7,8,9].

It is widely accepted that affective symptoms are the most prominent clinical features in "steroid psychosis" [10,11]. Lewis and Smith [12] reported in 1983 that there were seven mania, one depression and two psychosis in their original series. They also cited 60 mood disorders and 11 psychoses from their review of the literature. Ling *at al*. [10] found 45 patients with mood disorder and 9 with acute psychosis. Some previous reports of steroid psychosis [3] also demonstrated a higher incidence of depression than mania.

Female sex, systemic lupus erythematosus and high doses of prednisolone may be risk factors for the development of a steroid-induced psychiatric syndrome. Age does not appear to be a risk factor for the development of steroid-induced psychiatric syndromes. Adverse psychiatric reactions to steroid therapy usually occur early in the course of treatment. This time clustering of psychiatric symptoms may be due to the dose-response effect of steroids and consequently it may reflect the prescribing pattern for steroids; that is, frequently administered an initial large dose and the subsequent tapering of the daily dose. The dose-response effect of prednisone on the induction of psychiatric symptoms was most clearly demonstrated in the Boston Collaborative Drug Surveillance Project where 676 patients on prednisone therapy were evaluated for the development of acute psychiatric syndromes [13]. These investigators found significantly increased incidence of psychiatric disturbances associated with an increase in the average daily dose of prednisolone. The evidence from our patients also supports this dose-response effect: only two of the patients with significant psychiatric syndromes received less than 40 mg/24 h of prednisolone before the onset of symptoms.

Our data are quite similar to those reported in a review of literature over 45 years ago [14,15]. These similarities suggest that the overall incidence of these disorders were not changed in despite of the differences in the type of steroids used, or other changes in prescribing practices.

Conclusion

In summary, combining our case reports with those in the literature, we were unable to find any significant correlation between the type of glomerulonephritis and the average daily dose of corticosteroids, the duration of treatment before the onset of symptoms, the duration of symptoms or type of psychiatric syndrome. Continuous support by psychiatrists and their close cooperation with other physicians will contribute for an improved quality of life of patients undergoing long-term corticosteroid treatment. Finally, physicians should carefully monitor patients for psychiatric and cognitive side effects of corticosteroid use.

Conflict of interest statement. None declared.

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