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BRIEF COMMUNICATION

TRICYCLIC EXACERBATION OF STEROID PSYCHOSIS

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Four patients in a series of 14 cases of steroid psychosis where steroids were used to treat disease not effecting the central nervous system, are reported. All demonstrated a predominantly affective mood change prior to initiation of treatment with tricyclic antidepressants by the primary physician. In each case, the patient's mental state deteriorated rapidly following initiation of tricyclics in mid-dose range (*i.e.*, 100 to 150 mg q.d.). These agents produced a qualitative change in the nature of the patient's psychosis rather than simply aggravating pre-existent features. All patients experienced visual hallucinations within 4 days of tricyclic administration. Persistent auditory hallucinations (two cases) became threatening, accusatory, and constant. The exacerbated psychosis cleared rapidly with the discontinuation of the antidepressant and the addition of a phenothiazine. Phenothiazines, in doses of 400 to 800 mg q.d., were necessary to reverse the symptoms of these patients. Phenothiazines were also required to produce a salutary effect in the 10 patients who did not receive tricyclics, but at an average dose of only 200 mg.

Steroids raise the effective blood level of tricyclics and alter central catecholamine movement across membranes. These changes may represent the mechanism for exacerbation of steroid psychoses.

Studies of psychotic reactions associated with glucocorticoid treatment have been concerned primarily with clinical presentation, not treatment (2–5, 8). The presence of lability, agitation, and depression in patients with a steroid psychosis may prompt the physician to consider the use of a tricyclic antidepressant. This paper presents the results of such treatment in four patients who developed a psychosis secondary to steroid treatment of diseases not demonstrably effecting the central nervous system. In each of these cases, the clinical picture deteriorated following administration of a tricyclic antidepressant.

METHODS

The following four patients were drawn from a series of 14 cases of steroid psychosis seen by two of the authors (R. H. and M. P.) over a 7-year period. All were treated on medical wards and seen in consultation; primary medical responsibility remained in the hands of the referring physician. In three of the cases, a tricyclic antidepressant was begun by the patient's internist prior to psychiatric consultation. In these three cases, we relied on the reports of medical and nursing staff to reconstruct the features of each patient's initial presentation. Once consultation was instituted, patients were followed on a daily basis. Because of the controversy regarding the clinical features that typify steroid psychoses (2–5, 8); extensive mental status examinations and clinical observations were recorded.

RESULTS

Case I. The patient was a 37-year-old female with a diagnosis of rheumatoid arthritis. Her premorbid adjustment was good with no personal or family history of psychiatric illness. She had previously undergone two uneventful courses of steroid treatment. On the day of admission, the patient received 100 mg of hydrocortisone

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p.o., followed by 10 mg of hydrocortisone p.o., q.i.d. for 5 days. On her 3rd hospital day she became psychotic. Medical considerations were deemed to outweigh the consultants' recommendations to discontinue steroids. On day 7 her dose of steroid was changed to 5 mg of hydrocortisone p.o., q.i.d. for 5 days. This was followed by 5 mg p.o., b.i.d. for 10 days. The average daily dose of steroid administered was 23.8 mg with a prepsychotic average daily dose of 60 mg.

During her psychotic episode, the patient fluctuated rapidly between a severely depressed mood and a hypomanic state characterized by pressured speech and flight of ideas. She seemed bewildered by her intermittent memory difficulties and her occasional loss of orientation to time and place. Particularly striking was her complaint of sensory flooding (*i.e.* hypervigilance, a sensation that all sensory stimuli, and sound in particular, were so strong that they threatened to overwhelm her). She experienced nonthreatening auditory hallucinations and expressed suicidal ideation. Her delusional system was both paranoid and grandiose. She experienced disturbances of both body image and bodily sensation.

Amitriptyline was begun by her internist at 100 mg q.d. Within 24 hours she developed intermittent, nonthreatening visual hallucinations. Her auditory and visual hallucinations subsequently became threatening in nature. Her agitation increased in severity and she began to experience episodes of panic.

Amitriptyline was discontinued on day 3 and chlorpromazine initiated by the psychiatric consultant at 100 mg p.o., q.i.d. for 5 days; it was then reduced to 100 mg p.o., h.s. Her memory and orientation difficulties as well as her sensory flooding diminished markedly by the 2nd day of chlorpromazine treatment; her agitation diminished and the panic episodes abated. The hallucinations first became nonthreatening and then disappeared by the 5th day of chlorpromazine treatment.

Case II. The patient was an 18-year-old male with Crohn's disease. His premorbid adjustment was sociopathic, with three arrests (disorderly conduct and breaking and entering) and a record of expulsion from school. The patient's father was alcoholic. The family history was negative for other psychiatric disorders. The patient received 40 mg of prednisone p.o. daily for 17 days, and was discharged from the hospital on steroids. He had previously received two uneventful courses of steroid therapy.

On the 9th treatment day the patient became psychotic with sensory flooding (*i.e.*, hypervigilance, hyperacusis, and the subjective sense of being overwhelmed by sensory stimuli) as the dominant initial feature of the psychosis. Moderately severe emotional lability, intermittent apathy and memory impairment, bewilderment, flight of ideas, depressed mood, spontaneous weeping, bodily delusions, and alternating episodes of pressured speech and mutism were present.

Imipramine, 150 mg p.o., h.s., was administered by his internist for 4 days. During this time, the patient developed visual hallucinations and became increasingly agitated, aggressive, and paranoid, feeling he was being punished by the Gestapo. The imipramine was discontinued and chlorpromazine, 200 mg p.o., q.i.d., was administered by the psychiatric consultant for 2 days. Symptoms cleared rapidly. The chlorpromazine was subsequently reduced to 400 mg p.o., h.s. for 3 days, then to 100 mg p.o., h.s. for 5 days. The patient was then maintained on 50 mg p.o., h.s. until discharged. Mental status upon discharge was within normal limits.

Case III. The patient was a 17-year-old female with refractory asthma. She had a marginal premorbid adjustment, exhibiting an inadequate personality characterized by poor school adjustment and inability to cope with stressful situations. No formal family history of psychiatric illness was obtained, although her mother was felt by the authors to be a hysterical personality. The patient had received eight previous courses of steroid treatment. During her third course of treatment, she developed a psychosis characterized by sudden mood swings, agitation (pacing, hand wringing, hair pulling), nonthreatening auditory hallucinations, and sudden, severe episodes of anxiety.

On admission, 40 units of i.v. ACTH were administered over 8 hours. She was simultaneously begun on 60 mg of prednisone p.o. daily. The latter was continued for 3 days, and then reduced by 5 mg each day for 11 days.

On the 2nd therapy day the patient became psychotic, with symptoms of severe distractibility, total insomnia, and emotional lability with episodes of pronounced weeping and agitation. These symptoms alternated with periods of hypomanic behavior characterized by pressured speech, grandiose delusions ("I am the Virgin Mary and can absolve all about me of their sins"), and flight of ideas.

Imipramine was begun at 100 mg p.o., h.s. by the referring physician. During the afternoon of the 2nd day of imipramine therapy, the patient was found wandering off the ward in a confused and agitated condition. She physically attacked the ward staff when they attempted to return her to her room, stating that God's voice had told her they were evil. Her confusion and agitation worsened over the ensuing 8 hours, during which time she reported sensory flooding and visual hallucinations. Imipramine was discontinued and chlorpromazine, 100 mg p.o., q.i.d., was begun by the psychiatric consultant. The patient's symptoms cleared dramatically during the following 2 days. Chlorpromazine was reduced to 200 mg p.o., h.s. Two days after the reduction of chlorpromazine dosage, the patient again showed signs of deterioration; her lability increased and the nonthreatening auditory hallucinations recurred. The chlorpromazine was increased to 400 mg p.o., b.i.d. for 5 days. Her rapid response to this dosage permitted reduction to 100 mg p.o., t.i.d. for 2 days, then to 100 mg p.o., h.s.

Case IV. The patient was a 26-year-old female with ulcerative colitis. She had an extensive psychiatric history but had never been considered psychotic. However, she was refractory to psychotherapy and on each of four previous contacts with a psychiatrist, terminated treatment within 9 weeks. She was emotionally labile and had previously been diagnosed by all therapists as a hysterical personality. Her family history was negative for psychiatric illness. She had had one previous uneventful course of steroid treatment.

On admission, prednisone, 20 mg p.o., q.i.d., was administered for 1 day, followed by 10 mg p.o., q.i.d. for 10 days. The dose was then reduced by 5 mg every 3 days. Her average daily dose was 31.6 mg; the average daily dose prior to onset of psychosis was 53.3 mg.

On the 3rd hospital day, the patient became psychotic, manifesting severe distractibility, intermittent memory impairment, partial insomnia (*i.e.*, difficulty falling asleep and sleep continuity disorder), disturbances of body image, apathy, agitation, and depression. She was labile, intermittently mute, and experienced sensory flooding, bewilderment, and intermittent nonthreatening auditory hallucinations. Depressed mood with nihilistic delusions, sobbing, prolonged periods of tearfulness, expressions of helplessness and worthlessness, hopelessness and suicidal ideation dominated the initial presentation.

Amitriptyline, 150 mg p.o., h.s., was begun by the psychiatric consultant, who thought she had an agitated depression. On the 3rd day of antidepressant treatment, the patient evidenced rapid deterioration. She experienced threatening, almost constant auditory and visual hallucinations of gigantic nurses who wished to dismember her. Amitriptyline was discontinued. She was begun on chlorpromazine, 200 mg p.o., q.i.d., for 5 days with marked improvement. The chlorpromazine was decreased to 100 mg p.o., q.i.d. for 14 days, then to 200 mg p.o., h.s. for 3 days, followed by 100 mg p.o., h.s. for 2 days. By the 9th day of chlorpromazine treatment, her sensory flooding and confusion had diminished markedly. By the 24th day, the patient was free of psychotic symptoms and chlorpromazine was discontinued.

DISCUSSION

In each of the four cases, a rapid deterioration occurred in the patient's clinical condition following the initiation of a tricyclic antidepressant at a midrange dose.

The tricyclic antidepressants produced a qualitative change in the nature of the patient's psychosis, rather than simply aggravating pre-existing features.

Within 4 days of the initiation of tricyclics, all of the patients developed visual hallucinations. In the two patients who had previously experienced auditory hallucinations, these changed, becoming threatening in nature and almost constant. Rapid clearing occurred in each case with the initiation of chlorpromazine.

It is noteworthy that in each of these cases, the psychosis developed rapidly and progressively within the first 9 days of steroid therapy (average 4.25 days). All patients had had previous therapy with steroids (total of 12 courses). Only one patient had experienced a previous psychotic reaction; that patient became psychotic during the third of eight previous courses, evidencing symptoms of lability of mood, agitation, anxiety, and nonthreatening auditory hallucinations. Three of the four patients had experienced psychiatric difficulties before treatment was begun, but their premorbid personalities had little influence on the nature of the symptoms they manifested during the psychosis. The presentations of these patients, in spite of their rapid fluctuations, were more similar than dissimilar. Case IV was somewhat unusual, with many of the features of an agitated depression, but her course, when treated with a tricyclic antidepressant, was similar to that of the other patients. The initial presentation of the psychosis in these four patients was not significantly different from that of the other patients in our series. However, their course following treatment with tricyclics was significantly different.

Consideration of the possible pathophysiology of this deterioration is intriguing. The tricyclics are known to change central catecholamine movement across membranes. Maas and Mendieks (7) have shown that in rat brain slices, incubation with hydrocortisone leads to a significant increase in the uptake of exogenous norepinephrine. Thus, the tricyclics may be deleterious for patients receiving steroids by exacerbating a disorder of central catecholamine flux. The presence of hypomania in all of these patients, and flight of ideas in three, is consistent with this hypothesis. It is also noteworthy that steroids increase the plasma levels of tricyclics by inhibiting their metabolism, thereby increasing their availability to central neurons at, perhaps, toxic levels (1). This may be particularly important for such agents as proprotriptyline, which is thought to have a therapeutic window.

The variable and rapidly changing presentation of steroid psychoses may create uncertainty in the clinician's mind as to the most appropriate drug treatment. In three of the four cases reported here, the primary physicians were most influenced by the pained, depressed appearance of these patients, in spite of the fact that many other symptoms not typical of endogenous depression were present. Consequently, they used antidepressants as their initial therapeutic. This is not surprising, since de la Riva (3), Goolker and Schein (5), Soffer (8), and Glaser (4) all reported affective changes, and particularly depression, to be major components of these psychoses. They may, however, also present as somewhat atypical organic brain syndromes, paranoid reactions, or schizophreniform psychosis. The rapid clinical changes in a patient's condition, characteristic of steroid psychoses, further cloud the diagnostic picture.

Hall *et al.* (6) have shown that steroid psychosis is most likely to occur in patients receiving daily doses of steroids in excess of 40 mg/day of prednisone or its equivalent and that these reactions occur most often (2:1 ratio) within the first 6 days of steroid treatment. They found no clear relationship between the symptoms or types of psychoses which developed and premorbid personality, previous psychiatric treatment, or a history of previous steroid psychoses, and felt that nothing was *characteristic* of the symptom presentations or course except its variability, and hence, considered it a "spectrum psychosis." During the course of the psychosis, the most likely constellation of symptoms to appear include: depression, emotional lability, anxiety, distractibility,

pressured speech, sensory flooding, insomnia, perplexity, agitation, auditory and visual hallucinations, intermittent memory impairment, mutism, disturbances of body image, delusions, and apathy. Sensory flooding was perhaps the most striking finding across all 14 cases (6).

These authors (6) have also shown that steroid psychoses can usually be well controlled with initial doses of 200 to 400 mg p.o. of chlorpromazine/day (or its equivalent). The four cases presented here suggest that if a steroid psychosis is initially treated with tricyclic antidepressants, the required dosage of phenothiazine is higher and should be instituted at levels usually reserved for the treatment of a functional psychosis. Three of the patients here reported required doses of 800 mg p.o. of chlorpromazine/day, and the other required 400 mg.

These four cases raise serious question as to the use of tricyclic antidepressants in steroid psychoses. Other studies are necessary to clarify the question of whether these drugs are contraindicated in spite of the presence of affective symptoms.

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