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FEVER AND LEUKOCYTOSIS: PHYSICAL MANIFESTATIONS OF BIPOLAR AFFECTIVE DISORDER?

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Abstract

Kronfol, Ziad, Ghada Hamdan-Allen and Donald W. Black: Fever and leukocytosis: Physical manifestations of bipolar affective disorder? Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1988, 12: 887-891

1. Fever and leukocytosis are occasionally observed in patients with psychiatric disorders. A thorough medical evaluation does not always reveal the origin of these abnormalities.
2. We report the case histories of three patients with bipolar affective disorder and an abnormal DST who had fever and leukocytosis during the acute phase of their illness. No organic etiology could be found.
3. All three patients responded to ECT with resolution of the depression, the fever, and the leukocytosis, and normalization of the DST.
4. We propose that fever and leukocytosis may be rare physical manifestations of bipolar affective disorder, particularly in patients with abnormal DST.

Keywords: Bipolar Affective Disorder, Depression, Dexamethasone Suppression Test, Fever, Leukocytosis.

Abbreviations: Cerebrospinal Fluid (CSF), Computerized Tomography (CT), Electroconvulsive Therapy (ECT), Electroencephalography (EEG), Dexamethasone Suppression Test (DST), White Blood Cell (WBC).

Introduction

Fever and leukocytosis are not common manifestations of psychiatric illness. In fact, their occurrence in a psychiatric context usually alerts the physician to the possibility of an underlying organic etiology to the psychiatric disorder. A thorough medical workup often points to an accompanying infectious, toxic or neoplastic process that either causes or merely accompanies the psychosis. Treatment of the infection or other organic factor may result in the clearance of the psychosis. In many instances, however, no specific organic etiology for either the fever or the leukocytosis can be found. This situation leaves both the attending psychiatrist and the medical/neurological consultant uncertain about the origin of the fever and leukocytosis, and often results in a delay in the effective treatment of the psychiatric condition. We now present the case histories of three patients with affective disorder whose fever and leukocytosis seem to be related to their psychiatric illness per se and not to an accompanying medical or neurologic disorder.

Case Reports

Case #1

Mr. A is a 36 year old man with a long history of bipolar affective disorder. He was maintained on lithium prophylaxis, but poor compliance had resulted in multiple hospitalizations. On the day of admission, he was brought to the emergency room by the police because of inappropriate and disturbing behavior. Mental status exam revealed irritability, incoherence, racing thoughts, distractability, hypersexuality and auditory hallucinations. His lithium level was 0.12 mEq/l. Pertinent physical findings were an oral temperature of 36.8° C, a pulse of 136 and exaggerated deep tendon reflexes bilaterally. His white blood cell (WBC) count was 14,600 cells/mm^3 with 84% neutrophils. Medical workup including 6/60, 12/60, blood and urine cultures, cerebrospinal fluid (CSF) studies, chest X-ray, electroencephalography (EEG) and head computerized tomography (CT) were all normal. The dexamethasone suppression test (DST) was abnormal (Table 1). The patient met diagnostic criteria for bipolar affective disorder, manic type as established by the American Psychiatric Association's Diagnostic and Statistical Manual, Third Edition, 1980 (DSM-III). Treatment with lithium carbonate (with therapeutic blood levels) and neuroleptics was ineffective. He was therefore given a course of 6 unilateral electroconvulsive therapy (ECT) sessions. Following ECT, his mood became neutral,his psychosis had cleared, and both the fever and leukocytosis had resolved. A repeat DST was normal (Table 1). He was maintained on lithium prophylaxis with no further complications.

Case #2

Ms. B, a 20 year old woman with bipolar affective disorder, was maintained on trazodone and lithium carbonate. Ten days prior to admission, she became mute, noncommunicative, refused food and displayed waxy flexibility. Temperature on admission was 38.5°C and the WBC count was 19,500/mm^3 with 86% neutrophils. Lithium level was 0.75 mEq/l. The DST was abnormal. Laboratory investigation including 6/60, 12/60, blood, CSF and urine cultures, chest x-ray and head CT were all normal. The diagnosis of atypical bipolar affective disorder with catatonic features was made. The patient responded to a course of 8 bilateral ECT's with a complete resolution of catatonia, fever, leukocytosis, and normalization of the DST(Table 1). She was discharged on lithium and carbamazepine and her temperature and WBC count remained within normal limits.

Case #3

Mr. C, a 56 year old man with no prior history of psychiatric illness, presented with a two-month history of dysphoria, hypersomnia and generalized lack of interest. The initial mental status exam revealed depressed mood, psychomotor retardation and persecutory delusions. The DST was abnormal (Table 1). The diagnosis of primary affective disorder with mood incongruent psychosis was made and the patient was treated with desipramine 200 mg qhs, and haloperidol 20 mg daily. Five days later, he developed restlessness and insomnia, and exhibited euphoria, grandiosity and push of speech. Desipramine was discontinued and lithium carbonate 1200 mg daily was initiated. One week later, he became mute and diaphoretic and shot a temperature of 39.1°C. His WBC count was 14,900/mm^3 with a normal differential. Lithium level was 0.8 mEq/l. Chest x-ray, serologic tests, blood, urine, sputum and CSF

cultures were all negative. Head CT was normal. All medications were discontinued and a course of 12 bilateral ECT's was given. The mental status returned to baseline and the fever and leukocytosis cleared (Table 1). A repeat DST was not done. He was discharged on imipramine and fluphenazine with no recurrence of fever or leukocytosis.

Table 1

Temperature, WBC Count with Differential and Cortisol Values During the Acute Phase of Affective Illness and Following Recovery

	Case 1	Case 2	Case 3
Acute Phase			
Temperature (°C)	38.6	38.5	39.1
WBC Count (/mm^3)	14,600	19,500	14,900
WBC Differential (%)			
Neutrophils	84	86	71
Lymphocytes	9	6	24
Cortisol Values* (ug/dl)	19.4	10.1	19.8
Recovery Phase			
Temperature (°C)	37.3	37.0	37.2
WBC Count (/mm^3)	7,400	9,400	7,300
WBC Differential (%)			
Neutrophils	56	62	62
Lymphocytes	29	21	25
Cortisol Values* (ug/dl)	2.14	1.2	**

*the highest of two plasma cortisol values obtained at 0800 hour and 1600 hour the day following the administration of 1.0 mg of dexamethasone p.o. at 2300 hour.
**data not available.

Discussion

The three patients described above have several features in common. All three patients carry the diagnosis of bipolar affective disorder. They all had abnormal DST results. None of them responded to conventional pharmacotherapy including lithium carbonate, tricyclic antidepressants and neuroleptics, but all three responded to ECT. They all had a temperature of ≥ 38.5°C and a WBC count of $> 14{,}000/\text{mm}^3$ during the acute phase of their illness. Both fever and leukocytosis cleared with the affective episode following ECT. Fever and leukocytosis did not recur when lithium and/or other drugs were reinstituted prophylactically.

The etiology of both fever and leukocytosis is unclear. Common causes of fever and leukocytosis such as infection, toxicity or neoplasm were not evident. Furthermore, reversal of fever and leukocytosis with ECT argues against such etiological factors. Lithium carbonate has occasionally been associated with leukocytosis (Murphy et al., 1971), but hyperthermia does not usually occur except in cases of lithium toxicity, which was not the case in any of our patients. Leukocytosis without fever has also been reported in patients with manic illness who have never been treated with lithium (Kronfol et al., 1986). The neuroleptic malig-

nant syndrome is usually manifested by hyperthermia, increased muscular tonicity and may be accompanied by leukocytosis (Guze and Baxter, 1985). This syndrome however occurs in relation to neuroleptic intake. Only patient #3 had been on neuroleptic treatment (haloperidol 20 mg daily) when the fever and leukocytosis developed. This patient, however, did not exhibit increased muscular tone, a cardinal feature of the neuroleptic malignant syndrome. Catatonia can be accompanied by hyperthermia (Powers et al., 1976), but leukocytosis is not a typical feature (Regestein et al., 1977). Furthermore, catatonia is not a diagnosis in itself (Gelenberg, 1976) and is most commonly associated with affective disorder (Abrams and Taylor, 1976). The combination of lithium and haloperidol has been reported to produce neurotoxicity with fever and leukocytosis (Cohen and Cohen, 1974), but a careful review of these data indicate that the neurotoxicity was probably due to toxic lithium levels (Spring and Frankel, 1981). Fever and leukocytosis have not been reported to occur together as complications of lithium therapy when lithium levels were maintained within the therapeutic range.

We therefore propose that both fever and leukocytosis were physical manifestations of bipolar affective disorder. Temperature control and neuroendocrine regulation are both hypothalamic functions. The neuroendocrine system exerts considerable control over the hematologic and immune system, particularly the regulation of the traffic of leukocytes in the blood stream. More specifically, glucocorticoids increase the number of circulating neutrophils and decrease the number of circulating lymphocytes (Hills et al., 1948). Similar changes have been documented in patients with depressive illness (Kronfol et al., 1984), particularly those with hypercortisolemia (Kronfol et al., 1985). A possible clue to the hypothalamic-pituitary-adrenocortical link in the etiology of both fever and leukocytosis in our patients is that all three of them had abnormal DST results during the acute phase of their illness when fever and leukocytosis were evident. Once the psychosis had cleared, temperature and leukocyte count returned to normal, and the DST normalized in the two patients on whom results were available. No infectious, metabolic, toxic or neoplastic factor could be identified. Fever and leukocytosis may thus be an integral part of the illness in some patients with bipolar affective disorder, particularly those with abnormal DST results.

Conclusion

Fever and leukocytosis are occasionally observed in patients with psychiatric disorders. A thorough medical evaluation does not always point out the origin of the fever and increased WBC count. We report the case histories of three patients with bipolar affective disorder who, when ill, had fever, leukocytosis, and abnormal DST results. An extensive medical workup to determine the origin(s) of both fever and leukocytosis was essentially non-revealing. Both fever and leukocytosis cleared and the DST results normalized following successful treatment of the affective illness with ECT. We propose that fever and leukocytosis may be rare physical manifestations of the acute phase of an affective disorder, particularly if the disorder is accompanied by catatonic features and/or an abnormal DST.

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