Genetic Aspects of Manic-Depressive Disease in Family Practice

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Bipolar affective disorder (manic-depressive disease) is a mental disturbance characterized by phases of both depression and mania. Mania is essential to the diagnosis and is characterized by elevated mood, flight of ideas, and increased psychomotor activity. Current psychiatric literature not only shows that this disease is familial but has also demonstrated, through linkage studies, that an X-linked dominant mode of inheritance adequately explains the strong prevalence of bipolar affective disorder in some families.

The family discussed here shows many of the known clinical aspects of bipolar affective disorder. It serves as an example consistent with the X-linked dominant mode of inheritance.

Knowledge of the genetic background of this disease aids the family physician by helping to identify members of the family likely to have acquired this condition. The family physician can then look for future problems in them and in their offspring, leading to earlier diagnosis and more effective management. Thus, a member of a bipolar family with supposed unipolar illness (depression only) might be better served with the prophylactic use of lithium carbonate because of his likelihood of possessing a bipolar genotype. The prophylactic use of this drug has been shown effective in reducing the frequency, duration, and intensity of both manic and depressive mood swings.

Manic-depressive disease (bipolar affective disorder) has been and continues to be one of the most interesting mental disorders. Through its long and varied history, many disturbances have been included under its heading, such as schizophrenia, exhaustion stupors, hysteria, psychopathy, and paranoia. Modern definitions of this disorder all require the presence of mania in the illness. This is characterized by the symptoms of hyperactivity, euphoria, flight of ideas, distractibility, circumstantiality, and push of speech.[1] More simply, the three cardinal symptoms of mania are, (1) elevated mood, (2) flight of ideas, and (3) psychomotor overactivity.

Many studies have not differentiated between bipolar (manic-depressive disease) and unipolar disease (recurrent endogenous depression). Recently, however, a number of studies have shown clinical and familial differences. Patients suffering from bipolar disease tend to have earlier onset of the disorder. In one study, the onset in patients with manic-depressive disease was 34.6 years compared to 39 years in those with depression.[2] Other studies have borne out this finding.[3,4] Winokur, in agreement with other authors, has shown that first-degree relatives of manic-depressive patients, when compared to relatives of patients with only depression, (1) have a significantly higher prevalence of affective disorders in their families, (2) manifest mania more frequently, and (3) are members of familial constellations in which two generations of affective disorder are more frequently found.[5] Personalities are found to differ significantly between the two affective disorder subtypes. Manic-depressive persons were more likely to have active and sociable personalities, and depressive patients were more likely to score higher in insecure, obsessional, and sensitive traits.[6] Consistent with this, victims of manic-depression appear to be found more often in the middle and upper class socioeconomic groups. Several authors have suggested that bipolar affective disorder affects socially striving and potentially mobile individuals, who exhibit a great need for social approval and success.[7-9] It has been noted that both mania and depression can be found among relatives of bipolar patients, but significantly less manic behavior is noted among the relatives of patients with unipolar disease.

These familial differences suggest that the two affective disorder subtypes may be genetically different. Twin studies have shown a high concordance rate of mania in monozygotic twins. In affective disorders, only 25 percent of monozygotic twins show dissimilar types of affective illness, that is, one manifesting mania and the other showing only depression. Concordance for dizygotic twins is less than half that of monozygotic twins.[10] This suggests that there is a genetic factor present. Recent studies have shown bipolar families to have a pattern of inheritance of affective illness suggestive of X-linked dominance.[11-13]

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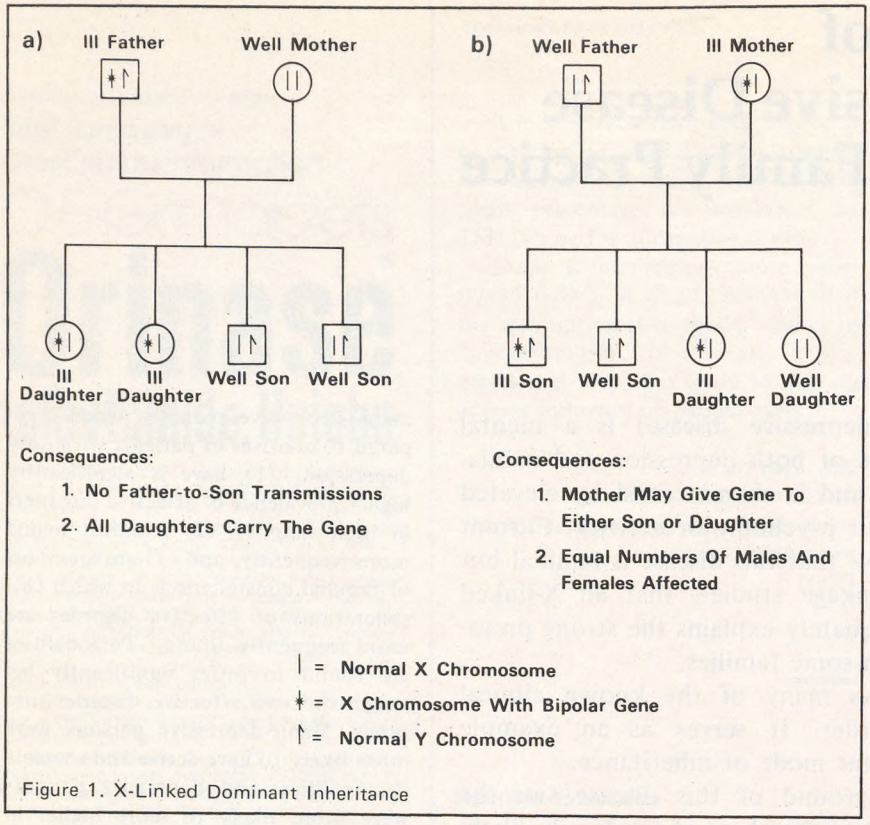

Figure 1. X-Linked Dominant Inheritance

For this mode of inheritance to apply to bipolar illness one would expect that overall more females than males should be affected. This has been shown to be true.[6,10,12] Another consequence of X-linked dominant inheritance is that ill males should have equal numbers of affected brothers and sisters and that ill females should have more ill sisters than brothers.[10] The absence of father-to-son transmission of illness is a crucial consequence of an X-linked dominant condition. (Figure 1a)

The most convincing evidence for X-linked inheritance thus far has come from genetic linkage studies. Xg^a blood group and color blindness can be used as X-linked genetic markers. Both Xg^a and protan and deutan color blindness are known to be carried on the human X chromosome. Winokur's group demonstrated just such a linkage. Within the families studied, a dominant X-linked gene seemed to be involved in bipolar illness transmission. Consistent with this, there were no father-son transmissions in 89 probands.[14] Other linkage studies have confirmed an X-linked transmission in many bipolar families. However, this cannot be generalized to all bipolar families because there are several series of bipolar families where known father-to-son transmission occurs[11] and which might perhaps have a different mode of inheritance.

The knowledge that unipolar and bipolar illness do indeed have different modes of inheritance is of prime concern to both the psychiatrist and the family practitioner since the advent of lithium carbonate. This pharmacologic tool has been used in the prevention of recurrences of mania successfully in several trials (some of them double-blind controlled).[14,15] It was found that lithium is effective in the prophylaxis of this disorder; it reduces the frequency, duration, and intensity of *both* manic and depressive mood swings.[16] However, its use in the prevention of recurrent endogenous depression (unipolar) has not shown it to be more effective than other currently available pharmacologic modalities.[17]

Secondly, knowledge of the genetics of this disorder might allow more accurate prediction of those members of a family likely to have inherited the genetic information and, therefore, the potential of exhibiting bipolar illness.

The purpose of this report is to present a case history of a family with bipolar affective disorder, showing how knowledge of the genetic inheritance helped the family physician in diagnosis and management of ill family members.

Family Case History

The following family has been seen in the Williamsburg Family Practice Office of the University of Iowa. The family pedigree (Figure 2) serves as an example consistent with an X-linked dominant mode of inheritance. The proband (David B) initiated his care at our office in 1973. At that time, he was suffering from an episode of mild depression. He had been hospitalized at age 31, in a Veterans' Administration facility, with a diagnosis of depression with paranoid and suicidal ideation. In 1973 (at age 41), a four to six-week period of hypomanic behavior (insomnia and some overactivity) was followed by a two-week period of frank mania in which he acquired a small farm, a boat, a motorbike for his son, and other items for which he had neither the need nor the means to pay. The family is in the middle class income range, the patient being employed as an insurance salesman. His sales in insurance would peak during this and all subsequent manic episodes, then fall in times of depression. The patient's family history was positive in that his grandmother (Figure 2: I,4) and his great aunt (Figure 2: I,5) both suffered from severe depression and also demonstrated periods of euphoria and great activity. His younger brother (Brian B) had been hospitalized on two occasions for "mental problems," type unknown. Further questioning elicited

the information that the patient's father was a former alcoholic and that his mother had experienced at least one episode of depression.

David B eventually required hospitalization for depression and was controlled with a standard regimen of antidepressants. He then began showing hypomanic behavior in November 1973, which culminated in his hospitalization in late December for alcoholic intoxication followed by a mild depression. The patient's insurance sales had skyrocketed throughout this period and continued to do so. He continued to drink excessively, was very hyperactive, suffered from insomnia, and was abusive to his wife. This again culminated in a depression in March and April of 1974, lasting four to five weeks, during which time he was admitted to an alcoholic treatment center where he was started on disulfiram (Antabuse). At about this time, we initiated his lithium therapy in an effort to control his bipolar disease. He was followed closely in our office, with frequent monitoring of serum lithium levels. The patient had no further episodes of manic or hypomanic behavior or depression until January of 1975, that is, ten months following onset of lithium therapy. At that time, the patient began to exhibit euphoria, unlimited energy, and rising insurance sales. No other abnormalities were noted and his serum lithium level was 0.87 mEq/liter (effective serum lithium level for maintenance usually ranges between 1.0 and 1.2 mEq/liter).

Nothing further was heard from the patient until the middle of March, when his wife reported that the patient was acting irrationally and was "very high." At that time the patient was euphoric, demonstrated push of speech, distractibility, and flight of ideas. He had not slept more than two hours a night for two or more weeks but had prevented his wife from seeking medical help. During this time he was selling huge amounts of insurance. His sales began to drop off only when he began to lose contact with reality. He was working all day selling insurance, helping his relatives farm until late at night, and then pacing the house all night, while his family tried to sleep. He was at that time attempting to evict tenants from his farm, and he purchased $30,000 worth of farm equipment with which to farm it himself. He had stopped taking all

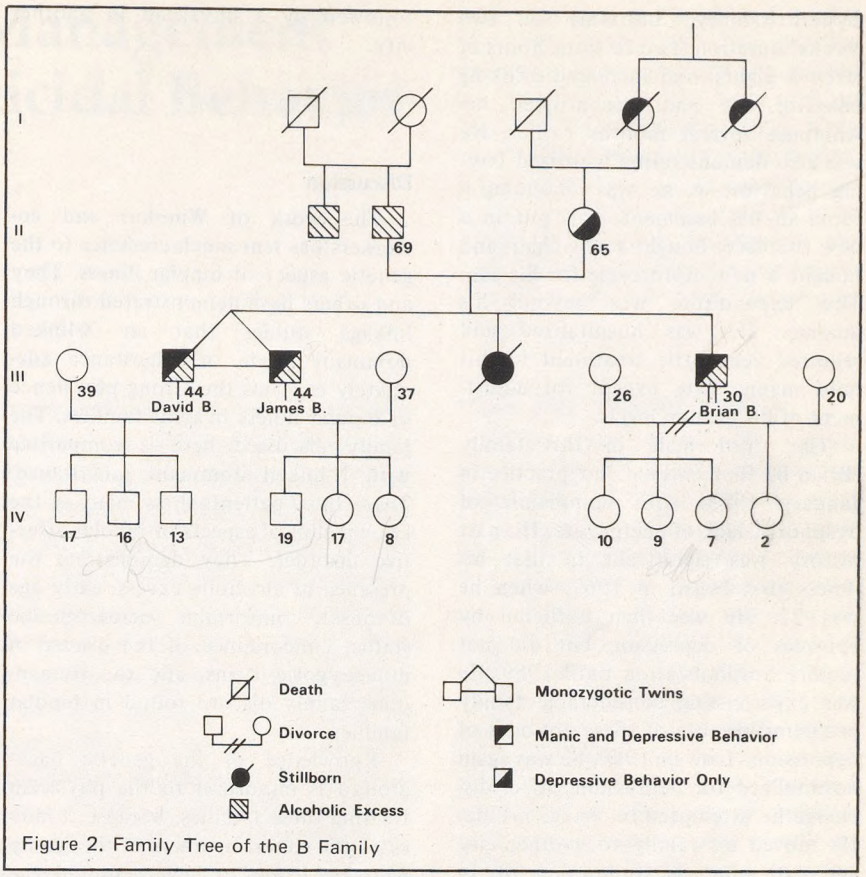

Figure 2. Family Tree of the B Family

medication. This resulted in hospitalization with haloperidol (Haldol) successfully employed to control his behavior. He was reinitiated on lithium and his serum lithium level raised to 1.25 mEq/liter. After his eventual control in the hospital and post-discharge, the patient did well until October and November of 1975, when he, again, demonstrated mild hypomanic behavior and his lithium level was adjusted during a short hospitalization.

This patient's monozygotic twin brother (James B) was first seen in our practice in November 1973, when he required hospitalization following a car accident resulting from excessive alcohol ingestion. He was suffering from depression and was treated appropriately. This patient stated that he began having episodes of depression or "lows," when he was approximately 32 years old. He reported alternate periods of euphoria and depression never severe enough to prompt him to seek medical assistance, until the car accident in 1973. During his periods of depression he would exhibit dysphoria, inactivity, much increased need for sleep, and lack of interest in his environment. During periods of euphoria or hypomania he would exhibit high energy levels, hyperirritability, insomnia, swearing, excessive alcohol consumption, and exaggerated buying behavior.

James B was not seen again in our practice until January 1975, when he was admitted to the alcoholic treatment center. There he was started on lithium because of the known bipolar history of his twin brother. He was also started on Antabuse. He did well until June 1975, when he required a short hospitalization for depression. In September 1975, he presented with

hyperirritability, insomnia of two weeks' duration (two to three hours of sleep a night), and increased drinking behavior. He had discontinued his Antabuse several months earlier. He was also demonstrating increased buying behavior, ie, he was rebuilding a room in his basement, had put in a new fireplace, bought a new chair, and bought a new motorcycle for his son. This expenditure was beyond his income. He was hospitalized and required very little treatment for his mild manic state except for adjustment of his lithium levels.

The third male in this family (Brian B) first entered our practice in January 1973, with complaints of dysphoria, lack of energy, etc. His past history was significant in that his illness first began in 1967, when he was 22. He was then bothered by episodes of depression but did not require hospitalization until 1969. He was experiencing considerable family problems because of these episodes of depression. Late in 1969, he was again hospitalized for depression. After discharge he attempted to change his life. He moved his family to another city and state where he took a new job. In 1970, he began to experience the feeling that he was stronger and better than he had been in his whole life; he had no requirement for sleep, and felt he could buy anything. This progressed to irrationality and he was hospitalized. After discharge he returned to Iowa for further hospitalization and treatment of his manic disorder. Shortly after this hospitalization and, as a consequence of his mania, he was divorced. In December 1973, he was remarried and, as stated above, was seen by us in January 1973, for symptoms of depression. Brian B was followed in our office until June 1974, when he began showing increased irritability, inability to sleep, and difficulty in concentrating. Ideas came into his head faster than he was able to put them into words. He was hospitalized and placed on lithium and chlorpromazine (Thorazine). In July of 1974, he was experiencing intolerable gastrointestinal distress and his lithium was discontinued. In August of 1974, he again developed manic symptoms including grandiose ideas, buying expensive objects, and drinking heavily. He was then restarted on lithium. He has since remained in relatively good control and is being followed by a physician in another city.

Discussion

The work of Winokur and coworkers has lent much credence to the genetic aspect of bipolar illness. They and others have demonstrated through linkage studies that an X-linked dominant mode of inheritance adequately explains the strong prevalence of bipolar illness in some families. The family discussed here is compatible with X-linked dominant inheritance. These three patients show many of the known clinical aspects of bipolar affective disorder. They demonstrate the presence of alcoholic excess, early age of onset, comfortable socioeconomic status, concordance of the disease in monozygotic twins, and the tremendous family discord found in bipolar families.

Knowledge of the genetic background is important to the physician treating these families, because it indicates the other members of the family who are likely to have acquired the gene. In the family discussed here, the known bipolar affective disorder in one twin (David B) allowed a more accurate diagnosis to explain his brother James' behavior than alcoholism alone, and suggested a more effective treatment: lithium. Also, all of the girls in Generation IV (Figure 2) would be expected to have received this gene. This alerts the family physician to look for future problems in them and their offspring, leading to earlier diagnosis and more effective management. How the gene will be expressed in these children cannot be predicted at this time. At present, none have clinical symptoms.

The management of this illness is certainly aided by a knowledge of the genetic transmission of this problem. A member of this family with supposed unipolar illness (depression only) might be better served with the prophylactic use of lithium, because of the likelihood of possessing a bipolar genotype. This cannot be proved in the family discussed here, because no linkage studies were done. The present illustration does demonstrate the efficacy of lithium in the management of bipolar affective illness, especially with the first patient discussed. Relapses do occur, possibly because of a low serum lithium level or the fact that lithium is not 100 percent effective. Current evidence indicates that these patients continue to go through cycles, but at a much lower frequency, with less intensity, and they are more easily managed.

Acknowledgement

The author would like to thank Dr. Robert Rakel for reviewing the article and for his suggestions.

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