

chapter 7

Discussion

Summary

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SUMMARY

Bipolar disorder, or manic-depressive illness, is a mood disorder in which episodes of mania, hypomania and depression occur in alternation with periods of normal mood, in any order over a lifetime. Bipolar disorder is a mostly recurrent illness associated with great morbidity. In the Netherlands, as in other western countries, both bipolar I disorder and bipolar II disorder have a lifetime prevalence of around 1%, while the overall prevalence of bipolar spectrum disorders is estimated to be around 5% (Ten Have et al., 2002; Regeer et al., 2004). A significant proportion of patients with bipolar disorder begin to experience their illness during adolescence (Goodwin and Jamison 1990). This is also confirmed by retrospective research in which adult patients with bipolar disorder report that they developed symptoms of their illness during adolescence and even childhood (Manzano and Salvador, 1993; Lish et al., 1994). A problem in these reports is the often long delay and therefore possible recall-bias. However, the majority of these patients suffer multiple mood episodes before being diagnosed, and this delay often has devastating and far reaching consequences for their relationships, education and employment. It is during this recognition lag that adolescents and young adults are expected to explore themselves and find their way into society. With the identification of risk factors, recognition, and management of the disorder possibly a reduction of impairment, improvement of social functioning and of employment stability can be accomplished. Bipolar disorder is highly familial; therefore offspring of parents with bipolar disorder provide an ideal group to study determinants of the bipolar disorder.

Children of parents with a bipolar disorder are the main topic of this thesis. Compared to children from healthy parents, these children have an increased risk to develop bipolar disorder as well as other mood disorders (Goodwin and Jamison, 1999). In order to learn more about the development of bipolar disorder, several questions need to be addressed. What are early symptoms of the bipolar disorder? What are the risk factors to develop a mood disorder? To find answers to these and other questions we started the study “Kinderen van Bipolaire Ouders” (KBO)-project (Dutch for “Children of Bipolar Parents”) which was launched by the end of 1997.

The focus of this thesis is on the impact of stress as a risk factor on the development of (bipolar) mood disorders among children of parents with a bipolar disorder (bipolar offspring). This overall theme of stress as a risk factor for (bipolar) mood disorders

is explored on different levels: as stressful life events associated with the onset of a first (bipolar) mood disorder and as immunological changes associated with the vulnerability or development of mood disorders. The course of psychopathology in this prospective study and the possibility to identify those subjects at very high risk to develop a bipolar disorder was studied as well.

In the various studies of this thesis the following research questions were addressed:

1. What is the prevalence and course of psychopathology, especially mood disorders among the offspring of bipolar parents during a nearly five-year follow-up period? (*Chapter 2*)
2. What is the impact of stressful life events on the development of mood disorders in adolescents? Are there possible decay effects? Is the impact of stressful life events on mood disorder onset modified by familial loading for mood disorders? (*Chapter 3*)
3. Is it possible to replicate and extend our prior findings regarding stressful life events, by collecting five year follow-up data on our cohort of adolescent offspring of patients with bipolar disorder? (*Chapter 4*)
4. Are there controlled studies in patients with bipolar disorder concerning cell-mediated immunity and thyroid autoimmunity? (*Chapter 5*)
5. Do bipolar offspring inherit from their parents not only the vulnerability to develop a mood disorder, but also the vulnerability to develop thyroid autoimmunity? If so, are these immunological aberrancies state or trait dependent? (*Chapter 6*)

Psychopathology as defined by DSM-IV was assessed during three measurements. Across these three measurements there was a gradual increase of psychopathology, which concerned especially life time DSM-IV mood disorders. The lifetime prevalence of any psychiatric disorder increased from 44%, via 49% to 59% of mood disorder diagnoses increased from 27% at first measurement via 33% at second measurement to 40% at the third measurement, and of bipolar disorders from 3% via 5% to 10%, respectively.

In our study at third measurement, twelve out of thirteen subjects with a bipolar disorder debuted with an initially unipolar (depressive) disorder at a mean age of 13.4 years (SD 4.2), i.e. at a mean of 4.9 years (SD 3.4) prior to their first (hypo)manic

episode at a mean age of 18.4 years (SD 2.9). Moreover, we can anticipate that in our sample over the next years the lifetime prevalence of these disorders will further increase. Finally, we found that so far almost all subjects with a bipolar disorder debuted with a depression at a mean of around 5 years prior to their first (hypo)manic episode, indicating that depression in bipolar offspring is a risk factor for the further development of the bipolar disorder and at the same time the first sign of the development of bipolar disorder (chapter 2).

Stressful life events (SLEs) are established as risk factors for the onset of mood disorders, but few studies investigated their impact on the development of mood disorders in adolescents. Also the temporal process of onset of psychiatric disorders following SLEs remains poorly understood. Surtees and Wainwright (1999) showed clear evidence for the progressive decay in the adverse effects of SLEs over time.

The aim of this study among an adolescent high-risk cohort was to investigate the relationship between SLEs and the onset of mood disorders with different models for the degree to which the presumed effects of SLEs diminish over time. In addition, it was examined whether this relation was modified by family loading for mood disorders. In our cohort of 140 adolescent bipolar offspring we assessed life events, current and past DSM-IV diagnoses and familial loading. To explore their interaction and impact on mood disorder onset, we constructed four different decay models. The relationship between life events and mood disorders was described optimally with a model in which the effects of life events gradually decayed by 25 % per year. The effect of life event load was not significantly stronger in case of high familial loading. In this study a strong relationship between life events and the risk of mood disorder in the offspring of patients with bipolar mood disorder was demonstrated. But familial loading did not confound or modify the relation between life events and mood disorder in this study. Both had independent effects on risk of mood disorders. The time span in which these SLEs were retrospectively measured was between 7 and 16 years (chapter 3).

Another study replicated the earlier found impact of SLEs on the onset of first mood episodes in adolescent and young adult bipolar offspring by now using the five year follow-up data of two subsequent measurements. The life event load remained significantly associated with an approximately 10% increased risk of mood disorder per unit life event load during the additional follow-up period. To rule out the possibility that these results are explained mainly by events that occurred before

first measurement we also analyzed separately the effect of SLEs during the follow up period. Even then, and with only 15 subjects developing a first mood episode, the same significant hazard ratio of 1.1 was found. Moreover, we found that the effect was significant for the offspring who had developed a bipolar disorder. As in the previous study, familial loading for mood disorders did not modify the association of SLEs and onset of mood episodes. Possibly that is because of the lack of power. However, this study suggests that there is no evidence of gene-environment interaction concerning familial loading and SLEs (chapter 4).

The role of the immune system in psychological stress has also been extensively studied over the past decades (Connor & Leonard, 1998). The impact of psychological stress on the immune system is far more complex than the common notion that stress suppresses immunity. Although this may be true for chronic stress, acute stress can definitely enhance immune function. The latter is congruent with the assumption that the immune system serves adaptation. Both clinical and experimental studies indicate that acute major depression is associated with an acute phase response and with an altered set point in the cell-mediated immune (CMI) system. As an introduction to chapter 6, the present review (chapter 5) focused on two aspects of immunological changes in bipolar disorder. First, the changes in the CMI system in bipolar disorder. Second, the relationship of bipolar disorder with thyroid autoimmunity, since impaired thyroid function has been associated with a worse outcome of mood disorders. Based on the controlled studies reviewed, concluded was that bipolar disorder seems associated with an acute phase response and activation of the cell-mediated immune system, and with an increased prevalence of antithyroid auto-antibodies. This close interaction between the immune system, the endocrine system and the central nervous system may provide new clues to the understanding of mood disorders.

In chapter 6 the results of our prevalence study of autoimmune thyroiditis in offspring of bipolar patients are described. In a recent study on a large sample of outpatients with bipolar disorder we found the prevalence of autoimmune thyroiditis (as evidenced by a higher prevalence of antithyroid antibodies) and of thyroid failure (as evidenced by a raised serum TSH) higher than in the general population and disease controls (Kupka et al., 2002). Hence we considered thyroid autoimmunity more likely to be a “trait marker” of bipolar disorder than a “state marker” of an episode (Kupka et al., 2002) and

these findings thus raised the question whether thyroid autoimmunity is related to the disease itself or to the vulnerability for bipolar disorder. TPO-Abs were predominantly found in female bipolar offspring, who had a significantly higher prevalence of positive TPO-Ab titers (9 out of 57 female offspring subjects) as compared to the female high school and young adult comparisons (4 out of 103 female control subjects). In TPO-Ab positive offspring (n=11) a raised prevalence of 55% of thyroid failure (i.e. a raised serum TSH or l-thyroxine treatment) was evident. TPO-Ab positive offspring did not show a raised prevalence of mood disorders (or any psychopathology) as compared to the TPO-Ab negative offspring. Our study suggested that bipolar offspring are more vulnerable to develop thyroid autoimmunity independently from the vulnerability to develop psychiatric disorders. Moreover, our data on the high prevalence of thyroid autoimmunity in bipolar patients and their offspring (in the latter not associated to any psychopathology) underscore the systemic character of bipolar disorder and suggest common inheritable molecular aberrancies in both brain and immune cells involved in the development of these disorders or may be even combined “syndrome”.

Chapter 7 discussed the most important findings and conclusions of the current studies. This chapter ends with strengths and limitation, clinical implications and presents recommendations for further research and a fourth measurement on this high risk cohort.

The studies described in this thesis concerned the first, second (after 14 months) and third (after 41 months) measurement of the KBO (Children of Bipolar Parents) project. These studies have contributed to a better understanding of the development of psychopathology, especially mood disorders, among these children. Almost all bipolar subjects developed an initial depressive episode. Indicating that depression in bipolar offspring is a risk factor for the further development of the bipolar disorder and at the same time the first sign of the development of bipolar disorder. Several determinants in the development of the bipolar disorder have been investigated in these studies. Both stressful life events and thyroid abnormalities, contribute substantially to the biological and psychological vulnerability of this bipolar offspring cohort. Therefore they might be important determinants in the development of the bipolar disorder.

Considering these findings, it is important to closely monitor children of bipolar patients on the development of bipolar disorder, especially when they have mood problems or depressive symptoms. Clinicians should extend their interventions beyond mere treatment of mood symptoms. They should also pay attention to prevention and rehabilitative interventions, especially in people at high risk to develop the disorder, such as the offspring of patients with bipolar disorder. Altering or improving coping strategies could be a target for selective prevention in this population who are at high risk of developing a bipolar disorder. However, there is not much known about the efficacy of prevention and intervention strategies; this needs further investigation. In addition, our data on the high prevalence of thyroid autoimmunity in bipolar patients and their offspring underscore the systemic character of bipolar disorder and suggest common inheritable molecular aberrancies in both brain and immune cells involved in the development of these disorders. Despite being the largest study of bipolar offspring so far and despite being one of the few studies with a longitudinal design so far, several questions remain. Large, and long-range follow-up studies that tracks probands across transitional developmental stages are very important to facilitate research on this topic. Therefore, extensions of our study with a longer follow-up (i.e. a fourth measurement) as well as with more participants (i.e. the selection of another younger offspring cohort) are highly recommended.