

chapter 7

Discussion

Summary

Samenvatting

Dankwoord

Curriculum Vitae

GENERAL DISCUSSION AND CONCLUSION

Recapitulation of research questions

The KBO (Children of Bipolar Parents) study started in 1997 by determining the prevalence of psychopathology among children of bipolar parents in the Netherlands. The reported prevalence in other studies of children of bipolar parents varied greatly (see chapter 1, table 2). This was probably due to methodological differences between studies, e.g. variation in sample composition and differences in diagnostic procedures (Wals et al., 2001). At the second measurement in 1999 and at the third measurement in 2004 we determined the prevalence and incidence of psychopathology in this cohort again. Next, we examined the prospective course of psychopathology, especially mood disorders, to identify individuals at very high risk based on the course of psychopathology. Further, we investigated the impact of stress, measured as stressful life events with respect to the possibility of decay effect and modification by familial loading, on the onset of mood disorders. Also, immunological aberrancies (autoimmune thyroiditis) in this high-risk cohort were compared to the general population in order to investigate the hypothesized concept that the genetic vulnerability for bipolar disorder and thyroid autoimmunity are at least partially shared.

Specifically, the following research questions were addressed

- 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*)
- 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*)
- Is it possible to replicate and extend our prior findings by collecting five year follow-up data on our cohort of adolescent offspring of patients with bipolar disorder? (*Chapter 4*)
- Are there controlled studies in patients with bipolar disorder concerning cell-mediated immunity and thyroid autoimmunity? (*chapter 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*)

Prevalence, incidence and course of psychopathology.

In our study among children aged 16-26 years of bipolar parents we found at the third measurement that the level of psychopathology, mood disorders in general and bipolar disorder in particular, had increased compared to the first two measurements five and four years earlier. Lifetime prevalence rates of any mood disorder increased from 27% via 33% to 40% and of bipolar spectrum disorder from 3% via 6% to 10%. Moreover, a further increase of bipolar and probably also unipolar mood disorders can be expected in the coming years. Of the offspring with a lifetime DSM-IV diagnosis, 67% had a mood disorder at the third measurement.

Compared to our prior findings at the first two measurements, our current findings are more in line with other studies among bipolar offspring which reported high percentages of psychopathology in general and particularly of mood disorders (see chapter 1, table 2). Nevertheless, the lifetime prevalence of 10 % DSM-IV bipolar disorders in our study is still moderate compared to other studies among bipolar offspring in the older adolescent/young adult age range. These studies show a range of 3-35% of lifetime bipolar disorders in bipolar offspring. In terms of age distribution, our study population is best compared with the Canadian study of Duffy et al., (2002). They included 36 bipolar offspring subjects aged 10-25 years and found in 53% any psychiatric diagnosis and in 14 % a bipolar disorder.

Although it is generally well recognized that in the majority of bipolar patients the illness starts with one or more depressions (Goodwin and Jamison, 1990) our findings suggest that this is probably the case in almost all patients. When the illness starts with a full blown mania or severe major depression, such episodes are easily acknowledged, also retrospectively, as the debut of the illness. However, minor/mild depression or a hypomanic episode is often not recognized retrospectively, especially when they are overshadowed by subsequent more severe episodes. In our study because of careful diagnostics with its repeated assessments, probably most (if not all) mild mood disorders were detected. Therefore, our finding of a debut of bipolar disorder with a

depression indicates that in the bipolar offspring depression is an important predictor of bipolar disorder and can also be indicated as a substantial risk factor for developing a bipolar disorder.

Differences in prevalence and age of onset of bipolar disorder between European and US studies.

In our high risk sample, only 4 subjects with a bipolar disorder (30%) had their first depressive mood episode before the age of 12 and none had their first manic episode before the age of 12 (mean age 18 years, range 14-25 years). Thus, our study suggests that (1) most patients with bipolar disorder have their first manic episode in adolescence or young adulthood and not during childhood, and (2) in all but one patients with bipolar disorder the first signs were the development of a depressive episode and not a manic episode. This is in contrast with findings in the US, where many patients with a bipolar disorder have their first manic episode before puberty. Mean age at onset of bipolar disorder in a comparable US high risk study (Chang et al., 2000), was 10.9 years (SD= 3.2). Another recent study, using adult criteria for diagnosing bipolar disorder, that also reported a high percentage of patients with an early onset of bipolar disorder, is the US study by STEP-BD (Perlis et al., 2004). In that sample of 983 bipolar patients, 27.7% reported an onset of bipolar disorder before the age of 13 years and 37.6% between the ages of 13 and 18 years. The first episode of mood disorder was depression in 22.2% and mania in 56.8%; for the remaining 21.09% the precise pole of onset was not determined. However, a very important limitation of both the age of onset and of pole of onset determination of this study is its retrospective approach.

All published offspring studies (see chapter 1, table 2), with the exception of the studies by Chang and Duffy had a cross-sectional design. The limitation of such a design is that information on lifetime psychopathology and especially on its development, is subject to recall bias. Therefore, to better evaluate the development of psychopathology, studies with a prospective design with a long term follow up are to be preferred, as the study in this thesis.

There may be several reasons for the discrepancy in prevalence and age of onset of bipolar disorder. In a review article Soutullo et al., (2005), evaluated the international perspective on epidemiology and phenomenology and gave an overview of possible explanations for the US-Europe differences. First, research on child and adolescent

bipolar disorder in Europe and countries other than the USA is scarce. Second, there are important differences in methodology in the available paediatric bipolar disorder studies, such as range of age considered, rating scales used, and whether patients, their parents or both are assessed. Third, the recruitment (origin) of the sample, referred inpatients or outpatients or samples from specific or more general populations, may be another methodological difference. Fourth, actual criteria used to diagnose bipolar disorder may differ among countries. Differences in diagnostic criteria (DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10) may be relevant. Fifth, also the use of "softer" forms of the bipolar spectrum, such as bipolar II disorder or bipolar disorder Not Otherwise Specified (NOS), is more widespread in the US compared with European and other countries. Sixth, despite the lack of data it is possible that paediatric bipolar disorder (BD) is not diagnosed as frequently in Europe as in the US, partly due to clinician bias towards the diagnosis of attention deficit hyperactive disorder (ADHD), conduct disorder, major depressive or personality disorders instead of bipolar disorder. Seventh, bipolar disorder may indeed be over diagnosed in children in the US. These children may have what in Europe is called severe forms of ADHD with pronounced emotional deregulation or perceptual difficulties and/or irritability. This might especially explain the discrepancies in pre-pubertal prevalence of mania. For the diagnosis of prepubertal bipolar disorder many US researchers use the broader phenotype, including non-episodic, chronic, rapid cycling, mixed states, while in Europe the diagnosis of bipolar disorder is reserved for the narrower phenotype of classical bipolar I disorder with manias with euphoric rather than dysphoric mood (Nice guideline, 2006).

In our sample we could not confirm the high rates of ADHD or other behavioural problems. The lifetime prevalence of ADHD in the total offspring group was 5% and in the offspring with bipolar disorder it was 15%, compared to a life time prevalence of comorbid anxiety disorder in this group of 46%. One explanation might be that in our study children younger than twelve years were not included, possibly accounting for less reporting of past ADHD symptoms.

Impact of stressful life events on the onset of mood disorders

A life event is an environmental circumstance that has an identifiable onset and ending, and may carry the potential for altering an individual's present state of mental or physical well-being (Goodyer, 2000). There is now considerable evidence that undesirable life events do precede and increase the risk for depression in adolescents (Goodyer, 2000) and adults (Brown and Harris, 1978), how they exert their effects remains still unclear.

In the present study (chapter 3) a strong relationship between life events and the risk of mood disorder in the offspring of patients with bipolar mood disorder was demonstrated. The relationship was best described with a model in which the effects of life events steadily decay with 25% per year. While familial loading of unipolar disorder was significantly associated with the lifetime prevalence of mood disorders in our sample (Wals et al., 2004), it did not confound or modify the relation between life events and mood disorders. Both had an independent effect on risk of the development of mood disorders.

Few high-risk studies report the influence of SLEs as a risk factor for the development of a bipolar disorder. Johnson et al., (2000) concluded that bipolar patients with high constitutional vulnerability have an earlier age of onset and need less stress factors (early parental separation and life events) to become ill compared to unipolar patients. The Cardiff Depression Study (Farmer et al., 2002) investigated the suggested co-familiality of depression and life events and whether there might be a common familial factor influencing vulnerability to depression and the experience of life events. They reported, using a sib-pair design, no evidence for a common factor influencing both depression and life events. Kendler et al., (1997) showed that, in adults, negative life events were most likely to lead to onset of major depressive disorder in individuals inferred to have a genetic liability to depression. And also that the genetic liability to depression overlaps with the genetic liability to experience stressful life events. So, through their behaviour, people to some extent shape and select their environments. There is a lack of studies that have tested the role of gene-environment correlation and the role of gene-environment interaction in the development of depression from childhood into adulthood (Wals & Verhulst, 2005). To better understand the complex interplay between nature and nurture in the development of mood disorders in adults, future studies should ideally consider well measured risk environments in genetic sensitive designs.

Our findings are in line with the work of Wainwright and Surtees (2002), who developed sophisticated analytic approaches to study adversity-disorder relationships. Their study, like ours, showed that the simplest model, involving a single-time dependent covariate was inappropriate as it failed to capture the decay in the event effects but that an exponential decay of the adverse effects of life events over time had to be modelled. In studying the effects of negative life events on the onset of mood disorders in a high risk group of adolescents, Silberg et al., (2001) found that there was no effect of independent life events on adolescents' depression in the absence of parental emotional disorder, but a significant effect in its presence. In our sample all subjects had a parent with a bipolar disorder. As described, high familial loading was based on the number and age of unipolar affected first- and second-degree relatives of the adolescents.

According to our study the impact of SLEs principally accumulates, but at the same time the impact of a life event gradually decays (25% per year) as time goes by. This suggests that the effects of SLEs do not simply add up or rapidly extinguish but, in a gradually fading fashion, carry over into the future risk of an episode of mood disorder. What drives decay is not known. It might result from coping strategies, the effect of neutralising life events or simply the passing of time. While high familial loading for unipolar depression was strongly related to risk of mood disorder, it did not confound the relationship between life event load and mood disorder association. There was also no evidence suggesting that familial loading modified the relation between life event load and mood disorder.

In chapter 4 we report on the five year follow up data and the effects of stressful life events on mood disorder onset. This study replicated the earlier found impact of SLEs on the onset of first mood episodes as found at the first measurement (chapter 3) but now using the data of the two subsequent measurements. The associated risk of life events with the onset of mood disorders had remained the same also during the follow-up period. To rule out the possibility that these results could be explained mainly by events that occurred before first measurement, we also analyzed separately the effect of SLEs during the follow up period (i.e. between the first and third measurement). Even then, and with only 15 subjects developing a first mood episode, the same result 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.

Genetic influences on life events and mood disorders

Why does not everyone who experiences stressful life events develop a mood disorder? And why do some people seem to attract more adversities during their life than others? Psychiatric genetic research has reported significant heritability not only for mood disorders, but also for the liability to experience life events (Silberg et al., 2001).

The majority of depressions occur in individuals with longstanding difficulties in their life but only about 50% of depressive episodes in adolescents are preceded by highly proximal undesirable life events (Lewinsohn et al., 1995; Goodyer et al., 2002). The remainder show slower onsets over time, often with onsets occurring following rising levels of depressive symptoms. This suggests that a correlation between recent life events and depression may reflect a genetic susceptibility to both phenomena, making the interpretation that events alone cause depression, less likely. In such circumstances both life events and disorders may have been brought about by genetically mediated person-environment interaction. A recent twin study has shown, however, that recent stressful life events that are independent of an individual's behaviour, do have a substantial causal relationship with onset of major depression (Kendler et al., 1999). Findings from adolescent twin data suggest that there are two somewhat different genetic influences: first, a direct effect increasing the risk for depression independent of social experiences; and, second, an indirect effect increasing the liability for experiencing life events (Silberg et al., 2001). In contrast, the already mentioned Cardiff Depression Study (Farmer et al., 2002) found no evidence for a common factor influencing both depression and life events.

To our surprise, also our study did not find that familial loading confounded or modified the relation between life events and mood disorder onset. This despite the fact that high familial loading for unipolar depression was found to be strongly related to the risk of mood disorder in this offspring cohort (Wals et al., 2004). This finding was also not expected, because of earlier findings by Ormel et al., 1991 and 2001. These studies showed that in the presence of high neuroticism and/or difficulties, the depressogenic effect of stressful life events was substantial, suggesting effect modification.

Of course our finding may be explained by the fact that the group of adolescents with a mood disorder was relatively small in our sample with an even a smaller group developing a mood disorder during follow-up. Consequently, the statistical power to

demonstrate an interaction between life event-load and familial loading was limited. Nevertheless, research data argues for a partly genetically mediated general liability to experience undesirable life events that arise through the adolescent's own behaviour (Goodyer, 2000).

Autoimmune thyroiditis

Kupka et al., (2002) reported a raised prevalence (28%) of autoimmune thyroiditis, indicated by a raised prevalence of thyroperoxidase antibodies (TPO-Abs), in a large cohort of bipolar patients, compared to 5-15% in the general population. The raised prevalence of TPO-Abs in the patients was neither associated with the use of lithium or any other drug, nor with their mood state. Autoimmune thyroiditis (AT) is an endocrine autoimmune disease in which the immune system erroneously targets TPO and thyroglobulin and in which the thyroid cells are ultimately destroyed (Weetman, 2003). Clinically overt AT is – like bipolar disorder - relatively prevalent and figures range from 1–2% in western, iodine sufficient populations depending on age and gender; women over 40-50 years old are in particular affected. AT is – like bipolar disorder - considered to be a poly-genetic and multi-factorial disease.

In a recent study (Vonk et al., 2006) the thyroid autoimmune status of monozygotic and dizygotic co-twins of a bipolar index case was investigated. In the bipolar index twins the raised prevalence of TPO-Ab positivity was confirmed and a prevalence of 27% was found. Interestingly monozygotic co-twins discordant for bipolar disorder (thus not having bipolar disorder) also showed a similarly raised prevalence for TPO-Abs (27%, n=15), while dizygotic co-twins discordant for bipolar disorder had a significantly lower TPO-Ab prevalence of 17% (n=25).

In our study (chapter 6) we investigated the prevalence of AT in offspring of a bipolar parent. At the first measurement all 140 bipolar offspring (age 12-21 years) were assessed psychiatrically and blood was drawn to determine TPO-Abs. Blood samples of high school students (aged 12 –19 years, n=77) and young female adults (aged 20-35 yrs, n=52) were used as comparisons. At follow-up in 1999 and 2003 the offspring were again psychiatrically assessed and tested for TPO-Abs (14 months and 41 months after enrolment). TPO-Abs were more prevalent and of higher titer in the (female) offspring as compared to the controls at all three measurements. The increased prevalence of autoimmune thyroiditis in the offspring was independent from the presence of mood

disorders or of any other psychiatric disorder, at least during the time of follow-up. There are two explanations for this finding. First, it is of course possible that in time and with the development of more psychopathology in our bipolar offspring, autoimmune thyroiditis and bipolar disorder become associated. Alternatively however, our findings may suggest that both manifestations are to some extent independent from each other. Thus, 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 a common or shared genetic factor. Taken together with the above mentioned findings in the bipolar twins, AT could be a so called endophenotype for bipolar disorder (Vonk et al., 2006).

Strengths and limitations of the study

Our study has several (methodological) strengths:

1. A major strength of the present study above other bipolar offspring studies is the relatively large sample of bipolar offspring. As shown in chapter 1, our sample is the largest sample of bipolar offspring studied up until now.
2. Thanks to the prospective design of our study, the examination of longitudinal data in our study provided unique information in a population at risk. Because we had data on three measurements, we could determine the developmental course of for instance self-reported mood symptoms scored on continuous scales in this sample of bipolar offspring. Thus, it was possible to determine the onset and course of affective problems as well as the age at onset of the first DSM-IV mood episode in the offspring sample with more precision than in previous retrospective studies.
3. The follow-up retention rate of our study remained very high. At the second measurement after 14 months 132 of the 140 offspring (94%) participated again, and four years later, five years after at the first measurement, 129 (92%) still participated in the study.
4. Our study used different assessment procedures (questionnaires and interviews) and two sources of information (offspring and parents in chapter 2-4,6) in order to determine the level and type of psychopathology in adolescent children of bipolar parents.

5. For the assessment of life events, we used the investigator-based Teenage Bedford College Life Event and Difficulty Schedule (LEDS) (Brown & Harris, 1978, 1989). This is a semi-structured interview for assessing life events and long term difficulties. It collects detailed information about the event itself, the timing of its occurrence (date) and relevant contextual information for each event. Several studies have supported the reliability (e.g., interrater) and validity (e.g., multiple informant) of the LEDS exhibiting a variety of psychiatric symptoms (Brown & Harris, 1978, 1989; Ormel *et al.*, 2001). In spite of the time consuming way of assessing life events, this instrument is for now the golden standard of reliable collecting life event data, and is not comparable with self reporting life events checklists.

6. During our study we collected blood samples at all three measurements in order to examine immunological parameters in the offspring cohort and collected blood samples of an healthy control group of adolescents and young adults ($n=129$). We also collected and stored blood samples of biological parents of the offspring cohort in order to create a genetic database. These data has not yet been used for research.

Our study also has a number of limitations:

1. The most important limitation of our study is the lack of a control group or normative data for psychiatric interviews under the age of 18 years. This makes interpretation of the prevalence findings based on the K-SADS DSM-IV diagnoses difficult. For the DSM-IV lifetime diagnoses based on the SCID I normative data from the Dutch general population study NEMESIS were available, but not for the same age group.

For our research on the various determinants of psychopathology among children of bipolar parents a comparison sample was less an issue, since we compared subgroups of offspring within the sample, for example offspring with mood disorders versus offspring without any diagnosis. Nevertheless, a control group of adolescents/ young adults without a bipolar parent would have given more data to study the impact of stressful life events on the onset of mood disorders.

2. Another limitation, shared with most other studies of psychopathology in offspring of bipolar parents, is the lack of information on the representativeness of the sample (see recruitment, chapter 1, figure 1). More than two-third (73%) of the families was

recruited via a patient association (the Dutch Association for Manic-Depressives and Relatives, VMDB). Possibly, patients recruited via a patient association are the relatively good functioning patients as compared to those of the outpatient clinics. However, with regard to their own social functioning and severity of psychopathology, parents recruited via the outpatient clinics did not show significant differences in number of hospitalizations, age at onset first episode, number of manic episodes, social economic status and divorce rate, compared to parents recruited via the patients association.

3. Although our study is – to our knowledge – the largest ongoing bipolar offspring study, the sample size is limited and therefore some of our data may not have reached statistical significance. For instance, a reliable figure on the exact prevalence of autoimmune thyroiditis in the various groups was not established; in our experience over 250 subjects in each group should have been studied for a reliable and statistically testable prevalence figure. This is even more true for genetic analyses; even though we have collected DNA material of almost all offspring and their biological parents, we were not able so far to perform adequate analyses of these data because of power problems.

4. Despite the fact that our study is one of the few prospective studies of bipolar offspring with a follow-up, the follow-up interval of 5 years is still limited. Consequently, the number of bipolar disorder onsets during this period was relatively small (9 new cases, i.e. less than 7% of the total sample), resulting in limited statistical power to demonstrate significant associations, especially interactions. A longer interval with more disorder onsets would have increased the statistical power of the study.

Another consequence of the relative short follow-up is the uncertainty about the unipolar depressive disorder diagnoses in our sample, since it is clear that the group of recurrent depressives includes so far unknown bipolar subjects whose depression may develop into hypomania or mania at a later stage during follow-up. One factor in this is the long time elapsing between the onset of depression and a diagnosis of bipolar disorder. This period was more than 7.5 years in a retrospective study of Ghaemi et al. (1999), 8 years in a national survey of the NMDA (1993) in the United States and 5 years in our own prospective study. As we can expect several new cases of depression and bipolar disorder as well as changes from unipolar depressive disorder to bipolar disorder in our sample during further follow-up, this will change our predictions concerning the risk factors for the development of a bipolar disorder.

5. Another limitation of our study is the change of the diagnostic interview to assess DSM-IV diagnoses. At the first and second measurement we used the K-SADS-PL version, whereas at follow-up we used the SCID I interview. Because different instruments may lead to different results, this might explain the considerable increase in bipolar disorder. Nevertheless we are confident about this limitation, as both instruments are rather similar. The K-SADS-PL and the SCID I are both semi-structured diagnostic psychiatric interviews based on the DSM-IV. They also use screen questions to check the presence of the main symptoms of the disorder before going to more detailed questions. Both instruments provide lifetime assessment; asking about past and current episodes of the disorder. However, there are also differences. The K-SADS-PL is administered by interviewing the parent(s), the adolescent and finally achieving summary ratings which include all sources of information, compared to only one informant in the SCID. Thus, the main difference between the K-SADS-PL and the SCID I is this usage of the number of informants. Nevertheless, it is unlikely that this is an explanation for more bipolar disorders at the third measurement, as interviewing more than one informant tends to detect more rather than less diagnoses. Unlike most depressives, hypomanic subjects seldom complain of or suffer from their shifts in energy, activity and sleep behavior and tend to experience them as positive. Such changes are more likely first to be picked up and recognized by family and friends (Angst et al., 2003). Therefore, using only the child as an informant may have led to relatively lower and not to higher rates of bipolar disorder diagnoses.

6. A limitation of the study on life events is that all data were collected at a particular point in time. As a matter of speaking, we employed a longitudinal approach with a repeated cross-sectional design by dating the onset of episodes of mood disorders and the occurrence of life events. Subjects with a mood disorder could have been more inclined to remember life events than those without this condition, which would result in recall bias. Therefore, we restricted our analyses to severe life events and omitted the first five years of life.

To explore the possibility of recall bias, we divided the subjects with a mood disorder in current cases, i.e. at the time of the interview, and past cases and compared the life events reported in the preceding two years. If recall bias played an important role this would probably regard the current cases more than the past cases. The results of this analysis, however, showed that the mean threat scores were similar, i.e. 4.2 and

4.0 respectively. Also, in the second study on life events we extended our data with a five year follow up and could replicate earlier findings, indicating the validity of our in chapter 3 hypothesized decay model.

Implications of our study for further research

In our study, evidence was found that the offspring of bipolar parents have an increased risk of developing a mood disorder and especially bipolar disorder. During the five years follow-up we also found that the risk, i.e. the prevalence of bipolar and other mood disorders, had increased. Our study population is still relatively young; they were aged between 16 and 26 years at the third measurement. This means that it is to be expected that still a substantial percentage of the offspring will develop a mood disorder, including switches from unipolar depressive disorder to bipolar disorder in the upcoming years. Therefore, a longer follow-up (i.e. a fourth measurement) of this cohort is needed in order to determine which of the present findings will hold. A longer interval with more bipolar disorder onsets (up till now 9 new cases with bipolar disorder) will also increase the statistical power of the study.

Furthermore, a longer follow-up is needed to evaluate the long term course and to identify which factors are predictive for a more benign course versus a more chronic course with recurrences. Uninterrupted long-range follow-up that tracks probands across transitional developmental stages are also highly recommended in a review by Strober et al. (2006). We can expect that our cohort of high risk adolescents and young adults (aged 15-26 years at third measurement) will experience several more transitions e.g. graduation from high school, leaving home, relationships, marriage, pregnancy, parenthood and more. These stressful transitions might influence and even provoke mood episodes. On the other hand, our high risk cohort started with the youngest participants at an age of 12 years; possibly we missed some major transitional developmental stages in the period before the age of twelve. Therefore it needs consideration to compose a new high-risk cohort starting from an earlier age. Other motives to compose a younger cohort are the differences with our US colleagues concerning the prevalence of paediatric bipolar disorder, the high prevalence of co-morbid ADHD in their offspring studies. A new young high-risk cohort might give us the opportunity to examine a) the existence and incidence of paediatric bipolar disorder, b) the incidence of ADHD prospectively and c) to study the impact of transitional stages during childhood.

At present there is no empirical foundation to support any assumption about the long term course or outcome of bipolar disorder when it arises in adolescence. Do the major phenotypes that comprise bipolar disorder (bipolar I disorder, bipolar II disorder) remain stable over time in young patients or does disease expression change as they mature? As described in chapter 1 based on age of onset, three subgroups can be distinguished (Bellivier et al., 2001, 2003). In a follow-up of our cohort the subgroup described as having a typical onset (mean age of onset 25.1) can be compared to the described subgroup of early onset with a mean age of onset of 17.4 years (this thesis). According to available literature, one would expect that the patients with a typical onset would show a milder course, less deteriorating behaviour and more euphoric manic symptoms compared to the early onset. However, because of our relatively small number of cases in this cohort we could not study this. Hence, this would also be an interesting topic for a future high-risk cohort.

In our study on the impact of stressful life events, we only assessed the association between life event load and the onset of the first mood episode. Already in 1921 Kraepelin described that the first episodes of mania or depression are often precipitated by psychosocial stressors, but that with sufficient numbers of recurrences lesser degrees of stress are required, and episodes begin to emerge more spontaneously or autonomously. Post (1992) reviewed the literature validating this concept, which is called the kindling phenomenon. In recurrent depression, episodes often seem to arise without manifest life events. These 'endogenous' mood episodes arise independently of external stress factors (Kendler et al., 2000) and will provoke new depressive episodes. Partial remission and residual symptoms after a depressive episode seem to be strongly associated with relapse. With a longer follow-up it will be possible to study the impact of stressful life events on the course of illness and to compare the results with the impact of life events on the onset of episodes in the same cohort. Thus, our cohort gives the opportunity to test the kindling phenomenon. The hypothesis could be that with time the impact of SLEs on subsequent mood episode onset would diminish.

Several studies (Kupka et al., 2002; Vonk et al., 2006), including ours, showed that the genetic vulnerabilities for bipolar disorder and thyroid autoimmunity are at least partially shared. So far however, we have not been able to investigate whether the increased prevalence of autoimmune thyroiditis found in the offspring group is related to the thyroid autoimmune status of the bipolar parents rather than the non-bipolar parents, as we did not have the opportunity and funds to collect blood samples

of the parents in order to determine their TPO-Ab levels. Therefore, at a future fourth measurement it would not only be interesting to investigate which of the TPO-ab positive offspring subjects developed a mood disorder, but also to assess which of the (bipolar and non-bipolar) parents had an autoimmune thyroiditis. 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”. The so far different penetrance of mood disturbances and autoimmune thyroiditis is likely due to the co-effect of other inheritable influences and/or the effect of exposure to different eliciting environmental factors in line with the view that bipolar disorder and autoimmune thyroiditis are etiologically complex syndromes.

For further studies we may hypothesize that an underlying immune aberrancy acts as an endophenotype and constitutes this shared genetic vulnerability factor for bipolar disorder and thyroid autoimmunity. In other words; is it possible to predict a very high vulnerability for the development of bipolar disorder, based on immunological aberrancies?

Implications of our study for clinical practice

Our finding of a debut of bipolar disorder with a (mild) depressive episode in 92% of the cases with bipolar disorder in our cohort, indicates that bipolar offspring with a depression can be regarded at high risk for developing bipolar disorder. Therefore, clinicians should closely follow bipolar offspring with a depression. A good balance between the burden of being monitored by psychiatric services and the profits of early detection for the adolescents is very important and has to be evaluated regularly. The internet as an easy accessible medium for both adolescents and clinicians might be used as a tool to keep in contact and to evaluate mood symptoms by using questionnaires such as the General Behaviour Inventory (GBI) (Reichart et al., 2005). Also clinicians treating adult bipolar patients should be alerted by depressive or other mood problems in the offspring of their patients. Once these are (or appear to be) present, a full diagnostic assessment should be done in order to be able to start adequate treatment (pharmacotherapy and/or psychotherapy) as soon as the first (depressive) episode emerges.

Furthermore, although our study did not address treatment in general and the issue of antidepressant-induced switch to bipolar disorder in particular, literature and clinical experience suggest that clinicians should be cautious to use antidepressants as monotherapy in bipolar offspring with a depression. When they prescribe an antidepressant they should inform their patients and relatives about the possibility of a (hypo) manic switch, and they should closely monitor their patients during the first months of treatment.

In the present study a strong relationship between life events and the risk of mood disorder in the offspring of patients with bipolar mood disorder was demonstrated, (probably) independent from familial loading. It is therefore that 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. By intervening before the onset of full-blown bipolar disorder, the disorder may be prevented or at least ameliorated in its severity, preventing poor social and vocational functioning. A possible way might be to help patients to identify their prodromal symptoms and/or individual maladaptive coping strategies in stressful situations and try to change these coping strategies. (Wong & Lam, 1999; Lam et al., 2001).

One might even consider an intervention in the group of adolescents at high risk to develop a bipolar disorder (high familial loading for bipolar disorder and a depressive mood episode themselves) by training their awareness of risk factors such as the impact of SLEs, sleep deprivation, alcohol and drugs abuse and their recognition of prodromal symptoms. The recent literature (Christensen & Kessing, 2005) supports the utility of individual cognitive behavioural therapy and psycho-educational approaches in patients with mood disorders to adapt coping strategies and enhance medication adherence. In their review Christensen and Kessing (2005) concluded that most studies show that emotion-oriented and avoidance coping strategies are associated with relapse of depressive episodes. Conversely, problem-focused and task-oriented coping seem to be associated with a good outcome. Also, psycho-education, evaluation of family relations and rearing practices (communication training), and assistance with concrete and specific problems concerning living with a bipolar parent (problem solving), seem

to be highly beneficial to the adolescents and families involved. These topics are the main elements of the Family-Focused Treatment by David Miklowitz (2004, 2006). Family-focused treatment (FFT) given in conjunction with pharmacotherapy appears to ameliorate the course of bipolar disorder in adults. This treatment has recently been modified to address the developmental presentation of bipolar disorder among adolescents. Given the good results described in an adolescent population with bipolar disorder (Miklowitz et al., 2004, 2006), implementation of FFT modules for clinicians who treat adolescent bipolar patients has to be considered.

Final conclusion

In our study among children aged 16-26 years of bipolar parents we found a high lifetime prevalence of mood disorders in general (40%) and of bipolar disorder (10%) in particular. Moreover, a further increase of bipolar and probably also of unipolar mood disorders is to be expected in the coming years. Our finding of a debut with a depression in the vast majority of the bipolar cases in our sample indicates that in the bipolar offspring depression can be considered as a substantial risk factor for developing a bipolar disorder. Also, according to our study the impact of stressful life events on the onset of a first mood disorder principally accumulates, but at the same time the effect of a life event gradually decays (with 25% per year) as time goes by. This suggest that the effects of stressful life events do not simply add up or rapidly extinguish but, in a gradually fading fashion carry over into the future risk of an episode of mood disorder. Regarding biological data, we conclude from our study that bipolar offspring is not only more vulnerable to develop bipolar and other mood disorders, but also more vulnerable to develop autoimmune thyroiditis.

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.

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