The Caracteristics of Childhood Onset Depression According to Depressive Symptoms, Comorbidities and Quality of Life

Ph.D. Thesis

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Abstracts:

VI. Baji I., Mayer L., Kiss E, Skulteti D, Boda K, Gadoros J, Vetro A. (2007) Effect of the depressive symptoms and life events to the quality of life in a school population. *15th AEP Congress, Eur Psychiatry,* Vol.22-Suppl.1: S222 (IF:1.27)

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VIII. Baji I., Lopez-Duran N. L., Kovacs M., George C. J., Mayer L., Kapornai K., Kiss E., Vuga M., Gádoros J., Vetró Á. (2009) Age sex somatic complaints and symptom presentation in childhood depression in a Hungarian clinical sample. *International conference Sponsored by ESCAP* 22-26 August 2009 Budapest Abstract CD

Table of Contenet

Summary

Introduction: Childhood and adolescence major depression is an under-diagnosed mental disorder, which can be traced back to several causes: 1. the DSM-IV diagnostic system is not specific enough considering the age. 2. Comorbidities frequently co-occurring with major depression, may overlap symptoms, thus they are rarely or not at all recognised. A small number of studies have examined developmental differences in rates of specific symptoms across depressed children and adolescents. These studies do not show a uniform picture. Some researchers reported more somatic complaints among depressed children. The gender has an influence on the symptoms of major depression. Anxiety comorbidities co-occurs with major depressive episode in 40%, while disruptive comorbidies 10-80%. The mental disorders have the negative effect on the quality of life of children. QoL is the combination of objectively and subjectively indicated well being in multiple domains of life. The stressful life events contribution to depression. 1. I hypothesized that there are some developmental and gender differences in depressive symptom presentation. 2. The somatic symptoms are more frequent in earlier life. 3. The frequency of depressive symptoms is increased by psychiatric comorbidities. 4. Stressful life events affect quality of life adversely, and it is worsened by depression. **Methodes**: We examined the above hypothesis in three samples. Participants were children (ages 7–14) with MDD, and community control kids from elementary schools. Diagnoses (via DSM-IV criteria) and onset dates of disorders were finalized “best estimate” psychiatrists, and based on multiple information sources. The depressive symptoms and effects of comorbidities were examined in depressive sample, and the quality of life was examined in the community sample. **Results:** Six symptoms increased with age, namely: depressed mood, hypersomnia, psychomotor retardation, fatigue, thoughts of death, and suicidal ideation. Only psychomotor agitation was more frequent in younger children. Anhedonia, insomnia, hypersomnia, and somatic complaints were more frequent among girls, and psychomotor agitation was more frequent among boys. Depressed mood, sleeping problems, psychomotor retardation, suicidal symptoms are significantly more frequent in anxiety group. Irritability and psychomotor agitation is significantly more frequent in the disruptive group. Worthlessness is the most frequent in the disruptive group, and in this group it is the third most frequent symptom. The clinical depression influences the quality of life the most strongly, and the higher depression score goes together with a lower quality of life. Stressful life events influence the quality

of life directly and through the depressive symptoms indirectly. **Conclusions** there are some developmental and gender differences in depressive symptom presentation. Irritability is the most frequent criterion symptom. We also observed stable and elevated rates of irritability, which were concurrent with stable and low rates of anhedonia across all age groups. Somatic complaints should be considered an associated feature of the symptom profile of MDD in pediatric populations. Depressive symptoms are reported to have more negative effects on the quality of life than do stressful life events.

Abbreviations

MDD: Major Depressive Disorder

ADHD: Attention Deficit and Hiperactivity Disorder

ALR: Alternating Logistic Regression

CDI: Child Depression Inventory

CFS: Chronic Fatigue Syndrome

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Proposed revision

GAD: Generalised Anxiety Disorder

GEE: Generalized Estimating Equations

IGIS: Intake General Information Sheet

ILK: Invertar Lebensqualität Kindern und Jugendlichen (ILK)

ISCA-D: Interview Schedule for Children and Adolescents–Diagnostic Version

SD: Standard Deviation

SPSS: Statistical Package for the Social Sciences

QoL: Quality of Life

WHO: World Health Organization

1. INTRODUCTION

1.1. Major Depression in Childhood and Adolescence

Mental disorders are becoming more and more frequently a burden on modern societies. According to forecasts, in the next decade in the countries of the European Union one in every four people, including children, will suffer from a mental disorder. Of all the childhood mental disorders probably the best known and most frequent is the early onset major depressive disorder (MDD), which is a burden for both the individual and the society, as it causes a significant functional impairment in academic performance, development of social skills as well as peer relationship, and it is an important risk factor in developing drug use, smoking and suicidal behaviour, and is going to be a severe public health and economic issue of the next decade, according to WHO prognostics. In adolescence the number of deaths as a consequence of suicidal behaviour is 12% of total mortality (Birmaher et al.1996).

Before the 80s childhood and adolescent depression was thought to be rare. The semi-structured interviews brought the proper diagnostic results and the change in its judgement (Keenan 2004). Depressive symptoms and depressive disorders are more and more frequent in childhood as well as in adolescence. According to epidemiological studies the frequency of MDD before adolescence is 1-2%, while the symptoms concern 3-8% of the adolescents (Egger et al. 2006, Stalets and Luby 2006, Birmaher et al. 1996, Costello et al. 2003, Zalsman et al. 2006). The results of domestic and international studies prove that life-time prevalence of depression is 4-5% in case of children and 13-20% among adolescents (Vetro et al.1997, Birmaher et al.1996), which is nearly the same as in case of adults, and it means that adult depression begins in adolescence in most cases (Kessler et al.2001, Szádóczky 2000, Wittchen et al.1998). Studies in the last decades proved that the risk of mood disorders is increasing and it begins at an earlier age every time (Kessler et al. 1996). Before the age of 18, 20-25% of the adolescents have a depressive episode (Lewinsohn et al. 1993). Researches done in schools showed the probability of MDD of 10-30% of students (Allen et al. 2000, Davanzo et al. 2004, Larsson and Melin 1992, Poli et al. 2003, Aszmann 2003). The research performed by Kopp and her colleagues (1997) show that 5% of the 16-year-old girls and 1,3% of the boys had severe depressive symptoms in a Hungarian study. In case of Hungarian youngsters there are not too much concern about the frequency and pathomechanism of childhood depression (Pikó and Fitzpatrick 2001, Vetro et al. 1997). The studies dealing with children under the age of 11 are especially insufficient. Schoolchildren aged between 11.5 and

17,5 have been examined regularly since 1985 in Hungary as well as the part of the international research organized by WHO (Health Behavior of School-Aged Children, HBSC). 18% of the boys and nearly 30% of the girls examined by the short version of Child Depression Inventory during the 2002 survey were found to have points referring to depressive mood (Aszmann 2003). The various long term depressive symptoms adversely affect the children's accommodation and performance, as well as their behaviour and life quality. Teenage girls are endangered significantly. Analysing the data of the National Comorbidity Survey 20% of the cases of major depression turned out to begin before the age of 18 before 1965, while in the cohort research done between 1965 and 1974 it was 50% (Kessler et al. 1996). Costello and his colleagues (2006) found that major depression in childhood is not more frequent, it is only examined more intensively by the researchers. In the study of Poli and his colleagues (2003) one of every three schoolchildren showed depressive symptoms. During researches done by self-reported surveys children showing depressive symptoms had a bigger chance to be depressed in the next 12 months (Ialongo et al. 2001). On the basis of these data specialists regards the early diagnosis essential.

1.2. Diagnostical Difficulties

Nowadays diagnosing major depression is based on the criteria of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association 1994, 2000), which makes differences between cross-sectional and longitudinal clinical status among mood disorders. Accordingly we can speak about mood episodes and disorders. The DSM-IV classification system makes a minimal difference between the criteria of the early onset and adult depression. In case of children, irritability is a criterion symptom, which is the equivalent of depressed mood (Kovács 1989, DSM-IV 1994).

Major depressive episode (DSM-IV): 1. *Depressed Mood/ Irritability in childhood; 2. Anhedonia (criteria symptoms);* 3. Significant Weight Loss and Weight Gain; 4. Insomnia or Hypersomnia; 5. Psychomotor Agitation and Retardation;6. Fatigue or Loss of Energy; 7. Feelings of Worthlessness and Guilt; 8. Impaired Making Decision; 9. Thought of Death; Suicidal Ideation; Suicidal Plan and Suicidal Attempt. At least five of the symptoms mentioned can be observed during a two-week period. From the first two symptoms at least one is necessary to set a diagnosis (criteria symptoms). The symptoms cause clinically significant distress or impairment in social occupational, or other important areas of functioning. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug abuse, a medication) or a general medical condition (e.g., hypothyroidism), and the

symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one. Many depressed adolescent fail to cover the diagnostic criteria of major depression, their symptoms are not severe enough or they remain unrecognised by specialists as they are hesitant considering their symptoms, and they have relatively shorter episodes (Angold et al. 1999, Kessler and Walters 1998, Kessler et al. 1994, Lewinsohn et al. 1993, Lewinsohn et al. 1994, Keller et al. 1998). Childhood and adolescence major depression is an under-diagnosed mental disorder, which can be traced back to several causes: 1. the DSM-IV diagnostic system is not specific enough considering the age. The literature deals with childhood and adolescence major depression, and accordingly we can suppose that there are symptoms that may draw attention to major depression in early ages (Kovacs 1996, Weis and Garber 2003, Baji et al. 2009). 2. Comorbidities frequently co-occurring with major depression (40-70%) (Birmaher et al. 1996), may overlap symptoms, thus they are rarely or not at all recognised. The so called “clear” – not comorbid – diagnostic categories are considered to be exceptions (Tringer 1999).

1.3. Depressive Symptoms and Age

Prominent psychoanalysts stated in the 1960s that depression does not exist in childhood, because children cannot express guilt with their under developed superego. However, several studies not only state that depression exists in childhood, but they insist that it is similar, if not the same as adult depression (Carlson and Cantwell 1982, Puig Antich et al. 1979). During the examination of adult and childhood depression cases all the major depression symptoms turned out to be present in every age, but the frequency is different (Carlson and Kashani 1988, Roberts et al. 1995). According to Cantwell and Baker (1991) childhood and adolescence depression can be distinguished from adult major depression, they emphasise the consideration of age in spite of the fact that during the research each of the depressive symptoms was recorded in every age. Over the past 3 decades, a large body of research has shown that children and adolescents can meet diagnostic criteria for major depressive disorder as defined in standard diagnostic manuals (DSM-IV). However, questions have remained about the appropriateness of such criteria for younger age groups. Most questions concern 2 issues, namely, (1) Are *DSM* criteria for MDD able to accommodate age-related differences in the likelihood of particular symptoms, and (2) are there different symptoms associated with MDD as a function of a child’s age? Surprisingly, research on age and sex differences in depressive symptomatology with clinical populations is scarce, and our current understanding of these effects is mostly based on studies using small sample sizes that limit the identification

of subtle effects. A small number of studies have examined developmental differences in rates of specific symptoms across depressed children and adolescents. For example, Ryan et al (1987) reported that, compared to depressed children, adolescents with MDD were more likely to display hopelessness, hypersomnia, and weight gain/loss and less likely to display somatic complaints and psychomotor agitation. In a similar study, Yorbik and colleagues (2004) found that depressed adolescents displayed significantly higher rates of hopelessness/ helplessness, fatigue, hypersomnia, weight loss, and suicidality than depressed children. However, Mitchell and colleagues (1988) found hypersomnia to be the only symptom more frequent in clinically depressed adolescents than in depressed children. Carlson and Kashani (1988) in their research found irritability, anger and psychomotor agitation more frequent in childhood than in adolescence. Considering that children can express sadness less, in most cases they are characterised by irritability and bored mood in case of major depression (Brent and Birmaher 2002). In the study of Cooper and Goodyer (1996) in case of 13-year-old depressed suicidal attempts were not present, while the rate of attempts was 21% in case of 15-16-year-old ones. These studies do not show a uniform picture in connection with the symptoms that might be a help to set up a diagnosis in this age group (Kovacs 1996). Differences found in studies are to be attributed to the developmental changes, as well as may be related to significant methodological differences between the studies (eg: type and size of sample, diagnostic tools) (Ryan et al. 1987, Kovács et al. 1984, Garber et al. 1984). Furthermore, previous examinations of age differences have used pubertal status (pre- vs. post-pubertal) to subdivide the samples. Examining chronological age-related changes in symptom presentation continuously, rather than categorically, may reveal more subtle developmental effects on symptom presentation throughout middle childhood and adolescence. The conclusion is that the diagnostic systems are not precise enough to display the developmental differences related to the symptoms of major depression, which are not permanent in different ages, but the age specific symptoms have not been identified yet (Kovacs 1996). The general use of proper semi-structured interviews as well as the episodes and the examination of the most severe time span of the person helped the diagnostic process. The methodological changes mentioned make it possible to compare the different researches thus giving an impulse to further studies in this field. The data of this study were collected according to the semi-structured interview technics.

1.4. Somatic Symptoms

Somatic symptoms have a close connection with some anxiety disorders, like separation anxiety and panic disorder (Beidel et al. 1991), and they are really frequent in case of children having major depression (Carlson and Kashani 1988). In primary health care systems 2-10% of the children have somatic symptoms, in most cases headaches and abdominal problems (Cooper and Goodyer 1993). In case of children with somatic problems mental disorders were found significantly more often, the most frequent is major depression and anxiety (McGrath et al. 1983, Garber et al. 1990, Campo et al.1994). In a study among children and adolescents with major depression the physical symptoms occured two times more frequent as in controls, and among those having headaches more depressive symptoms were present than among the ones without headaches (Larsson 1990, Goodyer 1996). Several studies have examined the association between somatic complaints and depression in younger ages (Mitchell et al. 1988, Goodyer 1996), but yielded contradictory findings. For example, some researchers reported more somatic complains among pre-pubertal compared to post-pubertal children (Ryan et al. 1987), while others failed to find this developmental difference (Mitchell et al. 1988). Such discrepant findings may reflect that none of these studies has controlled for co-morbid anxiety, that could have affected the results, given the high rates of anxiety disorders among depressed youths (e.g., Kovacs 1996), and the strong association between somatic symptoms and anxiety in childhood (Ginsburg 2006). Chronic Fatigue Syndrome (CFS) has several psychiatric and somatic symptoms above fatigue, and it frequently occurs together with mental disorders. Many researchers treat it as a psychiatric disorder; indeed, some of them consider it to be the physical manifest of major depression. This theory is supposed by the facts that depression frequently has somatic symptoms, and that antidepressants are often effective in CFS. In case of children it is typical that fatigue and headache are severe, they often complain about interrupted / intermittent sleep or hypersomnia, poor concentration and psychomotor retardation may occur, especially in case of adolescents (Garralda and Rangel 2005). Childhood depression is often co-occurs with somatic symptoms, like headache, stomach ache and muscular and limb aches (Goodyer 1996). They mean further overlapping with CFS. These somatic symptoms are frequent in anxiety disorders above all, in this group the occurrence of fatigue is frequent, too. A further common point is that both MDD and CFS cause significant functional impairment. While in case of depression 2 weeks is enough, in case of CFS the symptoms have to be present for 6 months. However, if we take into account that the average span of depressive episodes in childhood and adolescence is 7-9 months, we can see that time criterion makes only a slight difference between MDD and CFS (Kovács

1996). What is more, CFS in case of children the 6-month span is considered too long by specialists. (Garralda and Rangel 2005). Somatic symptoms are not considered to be depressive symptoms in the diagnostic system used at present (DSM-IV), they are recorded only among the symptoms of some types of anxiety, such as separation anxiety, panic disorder, general anxiety disorder and over-anxious disorder (DSM-III). In spite of this all, on the basis of the previous examinations we can state that physical symptoms co-occur with psychological symptoms, and they are changing with the age, so the development has an influence on the appearance of the disorder. The present diagnostic system (DSM-IV) ignores the additional symptoms of childhood and adolescence major depression (Cooper and Goodyer 1993, Goodyer 1996).

1.5. Gender Differences

According to several international studies in the background of childhood depression in addition to genetic and biological factors psychosocial and environmental factors also play an important role. Among the socio-demographic factors age and gender have an influence on the symptoms of major depression (Angold és Worthman 1993, Angold et al. 1998, 2002). The boy and girl ratio is nearly equal with slight male dominance in childhood (Birmaher et al. 1996, Poli et al. 2003), at the same time in adolescence the number of depressed girls is double of that of boys (Angold et al. 2002, Cyranowski et al. 2000). The presence of the gender differences is proved by several data considering the symptoms of major depression. The vegetative symptoms like change in appetite and weight, sleeping problems, as well as fatigue are more frequent in case of girls (Silverstein 1999). Examination of sex differences in child and adolescent depression have generally focused on rates of diagnosis and severity of symptoms (Nolen-Hoeksema and Girgus 1994, Nolen-Hoeksema 2001), with only a few studies of rates of specific symptoms. For example, Mitchell and colleagues (1988) and Roberts et al. (1995) found no sex differences in rates of various depressive symptoms in a small sample of inpatient and in a small community-based sample of children and adolescents with major depression. However, studies with larger samples have reported sex differences in appetite and weight fluctuations. For example, Williamson et al. (2000) and Yorbik and colleagues (2004) found higher rates of weight gain, and increased appetite among depressed girls compared to boys. Ryan et al. (1987) however, failed to find sex differences in weight gain or appetite changes, although they found that pre-adolescent boys experienced more fatigue symptoms than pre-adolescent girls. Other studies found attention deficit more frequent in case of boys (Gaub and Carlson 1997, Bongers et al. 2003). On the other hand the

differences mentioned were not found in several studies comparing depressed boys and girls (Mitchell et al. 1988, Roberts et al. 1995, Santalahti et al. 2005). These inconsistent findings may be due to significant differences in sample sizes and possible cohort effects, as studies differed greatly in the decade of data collection. Considering somatic symptoms gender differences are present with girl dominance, and it is a tendency up to adulthood (Taylor 1996).

1.6. Comorbidities

Literature shows an unambiguous connection between major depression and anxiety disorders, as well as oppositional defiant disorder and conduct disorder (Axelson and Birmaher 2001, Essau 2003, Ford et al. 2003, Angold and Costello 1993, Costello et al. 1996). Psychiatric comorbidities worsen major depression significantly; they increase functional impairment, and the patients need psychiatric care more often (Goodyer 1996, Klein et al. 2008). The most frequent comorbidities with major depression are over-anxiety disorder and general anxiety disorder (Costello et al. 2004). Comorbid anxiety disorders occur in half to three-quaters of the children suffering from chronic fatigue syndrome (Garralda 1999, Carter 1995). Anxiety comorbidities co-occurs with major depressive episode in 40%, and its onset is earlier (Kovács 1996, Akiskal 1990), while disruptive disorders: attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder and conduct disorder) are present in 10-80% with behavioural disorder co-occurring in 20% with major depression (Ryan et al. 1987). The substance use disorder is 20-30% and usually MDD begins 4-5 years earlier (Birmaher et al. 1996). Among children and adolescents having major depression several age specific comorbidities are present, such as ADHD, enuresis and encopresis (Kovacs 1996). Comorbidities can co-occur, but we may define a longer time span to examine their presence, or we can examine life time comorbidity (Angold et al. 1999). Taking comorbidities into account and making it clear how they influence the symptoms of major depression is essential regarding the diagnostic process (Weis and Garber 2003). Like childhood and adolescence major depression, comorbidities are under diagnosed. For the proper diagnostic process symptom oriented semi-structured interviews are the most suitable (Kovács 1996). The data of the present study have been collected with ISCA-D, it is the semi-structured interview.

Mitchell and his colleagues (1988) compared adolescents having major depression with anxiety comorbidities to those without any comorbidities, and examining depressive

symptoms. Their results showed that anxiety comorbidity has an influence on the depressive symptoms, it may increase the frequency of some symptoms: psychomotor agitation, guilt, hypersomnia, change in appetite and weight. There is much convergent evidence that anxious symptoms during a depressive episode are associated with a longer time in episode (Coryell et al.1992, Fava et al. 2004). Suicidal behaviour, which is increased by a longer episode and is often connected to psychoactive drug use, is a frequent symptom of major depression (Ryan et al. 1987, Kovács 1996). Both the anxiety and the disruptive comorbidities increase the risk of suicidal behaviour (Sihvola et al. 2007), and anxiety disorders increase the risk for suicide attempts considerably more than any other individual DSM-IV diagnoses (Wunderlich et al. 1998). On the basis of these data specialist consider the early diagnosis essential, which can be promoted by the examination of the age specific properties of depressive symptoms (Kovacs 1996, Baji et al. 2009), and the effect of the comorbidities on these symptoms.

1.7. Quality of Life

The actual expression ‘quality of life’ was introduced by Pigeon in 1920. At first it was used with respect to the level of financial demands, but later the concept was focused on subjective and individualistic issues. The quality of life is both a holistic concept and also a scientific categorization, which can be defined in several different ways. According to the definition proposed by Wallander and Schmitt (2001): “QoL is the combination of objectively and subjectively indicated well being in multiple domains of life considered salient in one’s culture and time, while adhering to universal standards of human rights.” The quality of life can be used to assess the function-damaging effect of certain diseases and the effectiveness of curative and preventive treatments (Vetró et al. 2003). With respect to health care, we can divide the methods examining the quality of life into two groups: reports on the quality of life related to disease and that related to health. The former concept measures the level of the symptoms, and clinicians assess the results; the latter results in a wide-ranging, multi-dimensional assessment. In studying quality of life, if a subject performs a self-assessment, the result is more likely to be up to date. One must differentiate between objective and subjective QoL. Objective QoL focuses on the objective quality of the conditions in which children live whereas subjective QoL examines the children’s subjective satisfaction with their lives. The subjective quality of life is an evaluation of one’s life, giving information about happiness, the frequency of pleasant feelings, satisfaction with life and the relative lack of unpleasant feelings (Diener-Biswas-Diener 2000). In children however, researchers have different opinions as to the reliability of self-provided data. The importance of children’s self-

reported opinions are emphasized in the literature (Eiser and Morse 2001, Lawford 2001). Although studies show that there might be significant differences between the opinions of children and those of an external assessor; thus, for children combination of both types of assessments could be the most beneficial (Eiser and Morse 2001, Lawford 2001). According to the current literature, major depression has the most negative effect on the quality of life of children (Sawyer et al. 2002, Bastiaansen et al. 2004). Several researchers have studied the negative effects of mental disorders on the quality of life of children (Sawyer et al. 2002, Munoz et al. 2005). In Sawyer and colleagues's (2002) study, groups of 6 to 17-year-old children suffering from mental disorders and from chronic somatic diseases, as well as healthy controls, were compared from the point of view of their respective subjective quality of life. In case of children suffering from mental disorders, both parents and children considered their quality of life to be worse than did the members of the other two groups. Patients suffering from major depressive disorder were the ones who evaluated children's quality of life at the lowest level. In Hungary, an overall examination of the school population occurs in the course of a program called the Health Behavior of School-Aged Children (HBSC) (Aszmann 2003). Registration of the quality of life of the school-aged population is carried out every four years. The health related-quality of life was found to be worse with increasing age in girls. In the course of the program "Hungarostudy 2002", Kopp and colleagues performed assessments of the quality of life of young people older than 16 years. In the other study the depressive symptoms decreased the quality of life in young people (Aszmann 2003, Kopp and Kovacs 2006). Satisfaction felt in different fields of life is closely related to the presence or absence of mental disorders in childhood (Mattejat et al.1988, Vetró et al. 2003).

1.8. Stressful Life Events

Today, the causes of the development of depression, the risk factors, and effects of the symptoms on the lives of children and adolescents are the centre of much research.

One of the most frequently examined aspects of depression is the effect of stressful life events, whose contribution to depression has been proven in a number of studies (Birmaher et al.1996, Williamson et al. 2005). Even by themselves, stressful life events worsen the quality of life (Williamson et al., 1995, Reinherz et al., 2000, Piccinelli and Wilkins, 2000, Paykel 2001, Jaffee et al., 2002, Infrasca 2003, Gilman et al., 2003). Even by themselves, stressful life events worsen the quality of life (Kopp and Kovacs 2006). Examining the total number of life events among 15-18-year-old adolescents Csorba and his colleagues (1994) found that

with the age the number of life events increased. Significant connection was found between stressful life events and depression in clinical and community samples of children and adolescents (Williamson et al. 1998, Birmaher et al. 1996, Sund et al. 2003). Exclusively in case of girls was found connection between depression and total life events by Rudolph's cross-sectional (1999) and Ge's (1994) prospective researches. According to the prospective research of Silberg and his colleagues (1999) total life events predict clinical depression more intensely in case of girls than in case of boys. In the four-year-long longitudinal study of Ge and his colleagues (1994) it was found that girls after the age of 13 survived more stressful events than boys, and it was only in case of girls that stressful life events caused also higher risk of depressive symptoms.

2. AIMS AND HYPOTHESES

I studied the developmental changes in the symptomathology of childhood-onset depression and I used a uniquely large clinical sample of depressed children and adolescents in Hungary.

Our hypotheses:

1) I hypothesized that there are some developmental differences in depressive symptoms presentation. I used the age as a continuous variable.

2) I hypothesized that there are gender differences in the occurance of psychopathological symptoms.

3) I hypothesized that somatic symptoms are more frequent in earlier life.
4) I hypothesized that the frequency of depressive symptoms is increased by psychiatric comorbidities.
5) I hypothesized that stressful life events affect quality of life adversely, and it is worsened by depression.

3. METHODS

3.1. Participants

We examined the above hypothesis in three samples, the age and sex distribution can be seen in Table 1. We obtained written consent for participation signed by both parents and the child, in accordance with the legal requirements in Hungary and the University of Pittsburgh, Pittsburgh, Pennsylvania, USA. All study procedures and consent forms were approved by the University of Pittsburgh's Institutional Review Board and the Board of Ethics of Human Research of the Hungarian Council for Scientific Research in order to comply with both countries' ethical rules.

Table 1. Description of three different samples investigated in different studies

Samples	N	Boys	Girls	Mean age years
Depressed 1 sample	559	312	247	11.69(SD=2.0)
Depressed 2 sample	649	351	298	11.70(SD=2.0)
Community sample	2620	1160	1460	10.45(SD=2.2)

3.1.1. Depressed Samples

Children in the depressed sample were enrolled in a study of genetic and psychosocial risk factors in childhood-onset depression between April 2000 and June 2007. Children were recruited through 23 mental health facilities (7 of which had both inpatient and outpatient units) across Hungary, serving both urban and rural areas (Vetró et al. 2009). They provided services to at least 85% of the newly registered child psychiatry cases, giving us access to a significant portion of the referred population nationwide. Children presenting at each site were scheduled for a research assessment if they met the following criteria: 7.0 years to 14.9 years old, no evidence of major systemic medical disorder, not mentally retarded, had available at least one biological parent and a 7 –17.9 year-old sibling (required by the study's genetic component), and attained a predetermined cut-off score on one of various depressive symptom screens (e.g., the short version of the Children's Depressive Inventory, CDI) (Kovacs and MHS Staff, 2003). Children meeting these initial criteria were scheduled for a 2-part evaluation, conducted on 2 separate occasions, about 6 weeks apart, by different clinicians. The first part of the evaluation entailed administration of the "Mood Disorder Module" of a diagnostic interview (see measurement section), as well as the Intake General

Information Sheet (IGIS), a comprehensive demographic and anamnestic data form. Participants also completed self-rated scales (not included in the present report). To set the proper framework and facilitate recall, evaluations started with a semi-structured interview, designed to construct a “time line” for the patient from birth to the date of the assessment. Children who met DSM- IV criteria for mood disorder at the first assessment were scheduled for further evaluation. The second part of the assessment involved a full diagnostic evaluation and completion of maternal self-rated scales. Results of the assessments and associated documentation (e.g., psychiatric records) were subjected to final consensus diagnostic procedure (Maziade et al. 1992). Pairs of senior child psychiatrists trained as Best Estimate Diagnosticians separately reviewed all material and together derived consensus diagnoses. As described in connection with previous work (Kovacs et al., 1984a and Kovacs et al., 1984b), operational rules were used to define disorder onset and recovery, and “midpoint” rules were used to date onsets and offsets, if more exact dating was not possible. All interviews were audio taped. The interviews were administered by child psychiatrists and psychologists with practice in child and adolescent psychiatry, who completed 3 months of didactic and practical training in the semi-structured interview technique. They were required to reach an average of 85% symptom-agreement on 5 consecutive videotaped interviews against “gold standard” interview ratings provided by the trainers. Interrater reliability on ISCA-D symptoms was satisfactory (using audiotapes of interviews for n=46 pairs of raters). For MDD symptoms, kappas ranged from .64 to .88, with 80% of the coefficients at or above 0.70. For DD symptoms (using DSM-IV criteria), kappas ranged from 0.38 to 0.93, with 80% at or above 0.70. For Generalized Anxiety Disorder symptoms (the most common DSM-IV anxiety diagnosis), kappas ranged from 0.53 to 1.00, with 62.5% at or above 0.70. Similar inter-rater reliability coefficients were obtained for other ISCA-D disorders as well (Kiss et al. 2007).

3.1.1.1. Depressed Sample to Examination the Depressive Symptoms

Five-hundred and fifty-nine children (247 girls) were enrolled in a study of genetic and psychosocial risk factors for childhood-onset depression between April 2000 and May 2005. The youngsters taking part in this research had the diagnosis of major depression and had a depressive episode in the time of the interview. Supposing that to the analysis of the symptoms the episode in time of the examination gives the most accurate information. The mean age at evaluation was 11.69 years (SD=2.00 years). Ethnic composition was representative of the ethnic composition of Hungary: 93.9% white, 3.6% gypsy (Roma), 2.3% multiracial, and 0.2% African. (Table 1. depressed 1 sample).

3.1.1.2. Depressed Sample to Examination of the Effects of Comorbidities on Depressive Symptoms

Six-hundred and forty-nine children (298 girls) took part in the research. The participants had a depressive diagnosis between April 2000 and June 2007, and during the interview they had an episode. (The group includes the members of depressed 1. sample) The average age was 11.7 years (SD=2.00 years). The ethnic composition of the group was the equivalent of that of the average Hungarian population. The participants were divided into three groups according to the life time comorbidities co-occurring with the major depression. The first group had only major depression diagnosis without comorbidities (clear MDD group), the second one had some anxiety disorder together with the major depression (anxiety group), and the third one had disruptive disorder co-occurring with the major depression (disruptive group). (Table 1. depressed 2. sample).

Table 2. Gender rate and average age in the three comorbidity groups

Groups	**N**	**%**	**Boys %**	**Girls %**	**Mean age years**
Clear MDD	297	45.8	52.5	47.5	11.9 (SD=2)
MDD+Anxiety comorbidity	212	32.6	45.3	54.7**	11.9 (SD=2)
MDD+Disruptive comorbidity	140	21.6	80**	20	11.2 (SD=2)

*p<0.05 , **p<0.01,

As far as age is concerned, there is no significant difference between the groups, at the same time in the anxiety group the number of the girls is much higher, while in the disruptive group there are a lot more boys (p<0.0001 two-sample t-test).

3.1.2. Community Sample

In the second half of the academic year 2002-2003, in April and May we visited primary schools in Győr and near Győr and in Szeged, and we asked the headmasters to cooperate after informing them about the method and the purpose of our data collection – according to the rules of data protection regulations. We had the written consent of nine headmasters, so we examined the students of 4 schools in Győr, two schools near Győr and 3 schools in Szeged. We sent letters to the parents including questionnaires concerning the children's emotional life, mood and quality of life, as well as tests to be filled in by the participants. The parents were informed in a covering letter about the process and the purpose of the research, and about the fact that filling in the forms and sending them back to the school is considered

to be their approval of the participation of their children in the study. They were also informed that their children will surely miss the research should they fail to send in the questionnaires, and that their children can refuse the participation even though they approve it. The parents put their questionnaires in a closed envelope into a collecting box in the school, 67.4% of the parents sent back the forms agreeing that their children can take part in the research. The children filled in the questionnaires in their own class room making sure they do that without giving their names. The headmasters were prepared in advance about the purpose and procedure of the study and about the content of the test packet as well as about the technical details of the procedure. In some schools prepared psychology students had the children fill in the forms under teacher supervision. The questionnaires filled in by parents and children were identified with the help of codes. These numbers were known only by research staff and unknown by school staff (Mayer et al. 2005, 2006). Five thousand two hundred and twenty four questionnaires were sent out to the parents of these children. From the returned questionnaires, we were able to collect data from a total of 3521 parents (67.4%) and 2913 schoolchildren (55.7%). In what follows, data from 2620 of these 7 to 15-year-olds will be investigated, a group whose child and parental questionnaires were of particular relevance in respect of quality of life, depressive symptoms, and stressful life events. The mean age of the children participated in the present study was 10.45 years (SD=2.2 years). There were 1160 boys (44%) with a mean age of 10.30 years (SD=2.15 years), and 1460 girls (56%) with a mean age of 10.57 years (SD=2.25 years). The girls were on average older than the boys (p=0.003, two-sample t-test).

3.2. Measurements

3.2.1. Interview Schedule for Children and Adolescents Diagnostic Version (ISCA- D)

(Examination of depressive symptoms in the clinical sample)

We used the Interview Schedule for Children and Adolescents–Diagnostic Version (ISCA-D), which is an extension of the Interview Schedule for Children and Adolescents (ISCA) (Sherrill and Kovacs, 2000). ISCA-D is a semi-structured interview to assess lifetime psychiatric disorders and current psychiatric status in youths. The ISCA-D organizes symptoms into disorders, includes most DSM-IV Axis-I diagnoses and allows assessment of “current” and “lifetime” disorders. Hungarian interviewers have achieved satisfactory inter-rater reliability (Kiss et al, 2006). The ISCA-D is completed by interviewing separately the parent (or other adult informant) about the youth, and then the youth about him/herself. For

each symptom, the clinician thus has a rating derived from the adult informant interview and one from the child interview: the clinician's final rating of each symptom serves as the basis for diagnoses. During the study 15 symptoms of the major depression were analysed. Because the somatic complaint is not a symptom of the major depression, we used the fifth symptom (somatic complaints) during the data analysis of the Childhood Overanxiety Disorder (DSM-III-R).

3.2.2. Child Depression Inventory (CDI), (Examination of depressive symptoms in the community sample)

The most frequently used self-report questionnaire for assessing childhood onset depression is the Child Depression Inventory Short Form (CDI-S); it contains 10 items each with 3 response choices, and the score for each item is coded 0-2 (Kovacs 2005). The maximum of the depression scale is 20 points. Each item assesses the sadness, irritability, self-acceptance and social relations. The questionnaire can be used for assessing the depressive symptoms of 7 to 18-year-old children. The time to complete the responses ranged from 10 to 15 minutes. Population-based international studies expect clinical depression if the overall score exceeds the threshold value of 7 points (Davanzo et al. 2004).

3.2.3. Invertar Lebensqualität Kindern und Jugendlichen (ILK) (Examination of the Quality of Life in the community sample)

The ILK inventory (Inventar Lebensqualität Kindern und Jugendlichen) is a 7-item, (school, family, peer relations, alone activity, physical health, mental health, and global Qol) self-report questionnaire assessing the general quality of life of children and adolescents about during the last week; it was compiled by Mattejat and colleagues in Marburg (Mattejat et al. 1988). The questionnaire can be applied from the age of six and has versions for both children and adolescents. The questions for the two age-groups are similar, but the version for children includes more detailed descriptions. In the questionnaire, seven domains (school, family, peer-relations, alone activities, physical health, mental health, and global quality of life) are investigated. For example: If you are among children, how do you feel between them, how do they relate to you, do you have a great time with them? Frequency is rated on a five-point scale best, better, middle, rather bad, badly; in the children's version, possible answers are marked with faces: smiling, half-smiling, neutral, half-sad and sad ones. Following the German classification, 1 point denotes the best, and 5 points the worst quality of life. To aid comparison with results of other questionnaires, the total score is calculated by the following

procedure: (i) the score for each item (domain) is transformed from a 1-5 onto a 0-4 scale, (ii) the 7 converted sub-scores are summed, and (iii) this total is subtracted from the maximal 28 (QoL28) points. Thus for the final score, a higher total denotes better quality of life. The original questionnaire was adapted for use in Hungary by Kiss and colleagues (2007), and this version has been tested to provide its own validity and reliability data (Kiss et al. 2007). Data on quality of life were collected from children's self-reports.

3.2.4. Intake General Information Sheet for Children and Adolescents (IGIS) (Examination of Stressful Life Events in the Communitay Sample)

Demographic data was collected from the parents by a modified version of the General Information Sheet developed for the study of childhood onset depression in both studies (Kapornai et al, 2007). It is a fully structured interview with pre-coded item response choices, covering among others, demographic, family, developmental, physical health, and psychosocial history and characteristics, stressful life events, with the parent serving as informant. It was used as a structured interview in the depressed sample, and as a self-report questionnaire in the school sample.

The self-report form is a modified version of the interview form. We studied life events that influenced the general state, the mood and the behaviour of the children according to literary data (e.g. illness or death of a relative, divorce and violence). We examined 26 stressful events. They were severe illness of a parent or a sibling demanding hospital care, severe health problem of a parent or a sibling, severe psychiatric disorder of a parent or a sibling demanding hospital care, death of a family member, divorce, significant financial problems, moving into a new home, unemployment of a parent, regular debates and quarrel between the members of family, birth of a new sibling, domestic violence, children boarded out, children regularly made fun of by their peers, children taken to police or court because of their behaviour, children expelled from school, survival of a natural disaster, loss of home.

3.3. Statistical Analysis

All data were normally distributed, therefore we used parametric tests. T tests were computed to explore differences between boys and girls, between age and symptoms and between sex and symptoms. Only significant interactions were included in the multivariate model. Since the results of the univariate models were redundant with those that emerged in the multivariate analyses, only the final multivariate models are reported

3.3.1. Symptom characteristics of MDD

Data analyses were performed using the SAS software. Chi-square test (Mantel-Haenzel $\chi^{2)}$ was computed to explore the effect of age on symptoms presentation and differences between girls and boys. Our large sample allowed for the simultaneous assessment of age and sex effects using alternating logistic regression (ALR), which controls for possible intercorrelations of symptoms within participants and provides robust, more reliably estimates than previously used methods.To estimate the effect of age, sex, and age-by-sex interactions on symptom presentation, we used alternating logistic regression (ALR; Carey et al. 1993) fitting a multivariate model of age and sex on the 16 symptoms of interest. ALR is a type of Generalized Estimating Equations (GEE; Liang and Zeger 1986). GEE methods is to be more efficient than ordinary logistic regression with variance correction for estimating the effect of a time-varying covariate. This method was initially created for analysis of inter-correlated cluster data (Katz et al. 1993) and has been extended to the analysis of inter-correlated outcomes (Kuchibhatla and Fillenbaumn 2005). The adjusted odds ratio of each symptom by sex and age while controlling for age, sex, and the correlation between symptoms.

3.3.2. Comorbidities and Symptom Characteristics of MDD

Data analyses were performed using the SPSS for Windows software, version 13.0. We used the Chi-square test, two-sample t-test. We divided the sample into 3 groups based on the comorbidities.

3.3.3. QoL, Stressful Life Events and Depressive Symptoms

Data analyses were performed using the SPSS for Windows software, version 13.0. Besides descriptive statistics, we used the Chi-square test, two-sample t-test and two-way ANOVA. Considering the number of experienced stressful life events, we divided the sample into 3 groups. The children who experienced 0-1 stressful life events are put in the first group, those who lived through 2-3 life events in the second group, and those who experienced 4 or more are in the third group. The relationship between the satisfaction of life quality and life events groups was analyzed by Chi-square test (with factors: [stressful life event groups] X [gender]. Gender differences of clinically depressed and non-depressed pupils' quality of life scores were also compared by two-way ANOVA (with factors: [clinically depressed groups] X [gender]). The indicators of the quality of life were analyzed by linear regression models, which allows those variables to be found which have a significant association with quality of life: depression mean scores, numbers of stressful life events, age and gender of the child, and

the interaction between depression scores and the number of stressful life events. The value of the Beta standardized coefficient can lie in the range between -1 and +1. The nearer the value is to either limit (-1 or +1), the greater effect it has on the quality of life. To decide whether stressful life events have an effect on the quality of life either directly or indirectly through depressive symptoms we used path-analysis. Path-analysis is a method by which we can examine relations between certain variables, and the direct and indirect effects of each variable on the others. In the path-analysis, we hypothesize relations between variables and the causal chains. In a certain sense, these are chains of regression models. In the representation of the path-analysis model, variables are connected with arrows, and the importance of the effect is signified by a number (standardized regression Beta coefficient) associated with each of them.

4. RESULTS

4.1. Study of Depressive Symptoms

4.1.1. Change of Frequency of Depressive Symptoms According to Age

Table 3 presents the rates of endorsement of each symptom by age.

Table 3. Unadjusted Rates (%) of Depressive Symptoms Across Age Groups

	Age at Interview								Statistic
	7	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**χ2**
Sample Size	**N=16**	**46**	**70**	**70**	**91**	**91**	**92**	**83**	
Depressed Mood	63	61	66	69	73	60	73	81	5.04*
Irritability	75	76	80	83	86	79	73	81	
Anhedonia	38	43	49	40	43	48	51	43	
Weight Loss	25	28	36	26	26	26	30	40	
Weight Gain	6	28	21	26	26	16	24	14	
Insomnia	63	46	60	49	63	55	55	57	
Hypersomnia	13	11	6	10	11	14	17	23	
Psychomotor Agit	63	52	56	53	45	36	39	43	7.70**
Psychomotor Retard	31	30	34	29	37	46	39	47	6.49*
Fatigue	69	41	60	63	64	70	67	70	7.57**
Worthlessness	44	50	59	57	59	63	60	63	
Guilt	25	35	41	33	31	35	30	35	
Imp. Decision Making	75	65	73	76	70	70	67	75	
Thoughts of Death	44	35	59	61	55	68	55	65	6.69**
Suicidal Ideation	25	17	34	39	41	44	45	49	13.87***
Somatic Complaints	50	35	36	29	37	35	43	35	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ Mantel-Haenzel χ^2

Depressed mood, hypersomnia, psychomotor retardation, fatigue, thoughts of death, and suicidal ideation increased linearly with age. Psychomotor agitation was the only symptom that decreased linearly with age.

4.1.2. Change of Frequency of Depressive Symptoms According to Sex

Table 4 presents the rates of endorsement of each symptom by sex. Six symptoms were significantly more common in girls than boys, namely: depressed mood, anhedonia, insomnia, hypersomnia, psychomotor retardation, thoughts of death and somatic complaints. In contrast, only psychomotor agitation was more commonly reported in boys than in girls.

Table 4. Unadjusted Rates of Depressive Symptoms for Girls and Boys

Symptoms	Girls(247)	Boys(312)	χ^2
Depressed mood	74.1	65.4	4.90*
Irritability	77.7	81.1	
Anhedonia	51.0	41.0	5.55*
Weight Loss	32.8	28.2	
Weight Gain	22.3	20.8	
Insomnia	61.1	51.6	5.08*
Hypersomnia	18.2	9.9	8.05**
Psychomotor Agitation	38.5	51.6	9.59**
Psychomotor Retardation	43.7	34.0	5.47*
Psychomotor Retardation	43.7	34.0	5.47*
Fatigue	65.6	62.8	
Worthlessness	61.1	57.1	
Guilt	33.2	34.3	
Impaired Decision Making	67.2	74.4	
Thoughts of Death	62.8	54.2	4.17*
Suicidal Ideation	43.7	36.5	
Somatic Complaints	42.1	32.1	6.01*

*p<0.05, **p<0.01 Chi-square test

4.1.3. Age and Sex Effects in Rates of Depressive Symptoms Adjusted for Inter-correlation between Symptoms

Table 5 shows the adjusted odds ratio of each symptom by sex and age while controlling for age, sex, and the correlation between symptoms. Results from the ALR indicated a significant effect of age $\chi^2(16) = 35.91$, $p = 0.003$ and sex, $\chi^2(16) = 38.65$, $p = 0.001$. No age by sex interaction was observed, $\chi^2(16) = 16.53$, $p = 0.42$. Consistent with the unadjusted results presented the 4 tables, and while controlling for sex and the inter-correlation between symptoms, the odds ratio of six symptoms increased with age, namely: depressed mood, hypersomnia, psychomotor retardation, fatigue, thoughts of death, and suicidal ideation. Only psychomotor agitation was more frequent in younger children. While controlling for age and inter-correlation between symptoms, being male significantly decreased the odds ratio of four

specific symptoms, namely: anhedonia, insomnia, hypersomnia, and somatic complaints, and significantly increased the odds ratio of psychomotor agitation.

Table 5. Odds Ratios of Each Symptom Adjusted for Age and Sex via Alternating Logistic Regression

Adjusted Multivariate Odds Ratio (95% C.I.)				
	Between-Subject by Symptom Effects			
Symptoms	**Age (Year)**		**Sex (Male)**	
Depressed Mood	1.10	(1.01 -1.21)*	0.71	(0.49 - 1.03)
Irritability	0.98	(0.88 -1.10)	1.22	(0.80 - 1.86)
Anhedonia	1.01	(0.93 -1.10)	0.67	(0.48 - 0.95)*
Weight Loss	1.06	(0.96 -1.16)	0.84	(0.58 - 1.22)
Weight Gain	0.94	(0.85 -1.03)	0.87	(0.58 - 1.31)
Insomnia	1.00	(0.92 -1.09)	0.68	(0.48 - 0.96)*
Hypersomnia	1.17	(1.02 -1.35)*	0.56	(0.34 - 0.93)*
Psychomotor Agitation	0.91	(0.83 -0.99)*	1.59	(1.12 - 2.24)**
Psychomotor Retardation	1.11	(1.01 -1.21)*	0.71	(0.50 - 1.01)
Fatigue	1.13	(1.03 -1.23)**	0.97	(0.68 - 1.39)
Worthlessness	1.06	(0.97 -1.15)	0.88	(0.62 - 1.25)
Guilt	0.99	(0.90 -1.08)	1.04	(0.72 - 1.49)
Impaired Decision Making	1.02	(0.93 -1.12)	1.43	(0.99 - 2.08)
Thoughts of Death	1.11	(1.02 -1.22)*	0.76	(0.54 - 1.08)
Suicidal Ideation	1.18	(1.08 -1.29)**	0.86	(0.61 - 1.21)
Somatic Complaints	1.01	(0.92 -1.10)	0.65	(0.46 - 0.93)*

* $p < 0.05$, ** $p < 0.01$, no sex-by-age interactions were noted.

4.1.4. Somatic Complaints and Psychomotor Agitation in Depressed Sample

Comorbidities may have an effect on depressive symptoms. In DSM-IV somatic symptoms are part of anxiety disorders. Given the historic interest in whether somatic complaints may be a presenting symptom in pediatric depression, we examined its rate among children without co-morbid anxiety disorder (N = 398). The rate of somatic complaints in this group was 29%, on average (range 20 to 46% across all ages), a rate higher than other depressive symptoms such as hypersomnia, weight loss/gain and guilt. Consistent with our full sample analysis, no age effects on somatic complaints were noted among children without co-morbid anxiety, χ^2 (1) = 0.53, p = .47. However, the sex difference in somatic symptoms in the full sample did not remain significant after controlling co-morbid anxiety disorder (33% in girls vs. 26% in boys), χ^2 (1) = 1.77, p = .18. Psychomotor agitation is also symptom of ADHD,

therefore the comorbidity with ADHD might change the incidence of that depressive symptom within the depressive sample. We also examined the rate of psychomotor agitation in children without co-morbid attention-deficit-hyperactivity disorder (ADHD; N = 449). Consistent with our full sample analysis, we found an age effect on psychomotor agitation (decreasing rates of agitation in older cases) even among children without co-morbid ADHD, χ^2 (1) = 7.19, p < .01. Finally, also consistent with our full sample analysis, boys were more likely than girls to present psychomotor agitation after controlling for co-morbid ADHD, χ^2 (1) = 10.13, p < .01.

4.2. The Effect of Psychiatric Comorbidities on Depressive Symptoms

4.2.1. The Incidence of Comorbidities in Depressive Sample

The frequency of comorbidities was as follows: Separation Anxiety 7.7%, Social Phobia 4.2%, Specific Phobia 3.7%, Agoraphobia 0.9%, Panic Disorder 2.0%, Posttraumatic Stress Disorder 3.1%, Obscessive Compulsive Disorder 2.3%, Generalised Anxiety Disorder (GAD) 10%, Childhood Overanxiety Disorder 10%, Anxiety Disorder Not Otherwise Specified 1.7%, Attention Deficit Hiperactivity Disorder (ADHD) 19.3%, Oppositional Defiant Disorder 4.6%, Conduct Disorder 3.4% and Disruptive Disorder Not Otherwise Specified 0.5%. It is obvious that the most frequent comorbidities were ADHD (19.3%), GAD (10%) and Childhood Overanxiety Disorder (10%).

4.2.2. Frequency of Depressive Symptoms in Relation to Comorbidities

On the bases of Table 6 we can see that irritability is the most frequent symptom in all the three groups. Studying the criteria symptoms (depressed mood or irritability, anhedonia), depressed mood is the most frequent in the anxiety group (67.5%, p < 0.01), irritability is significantly more frequent in the disruptive group (80.7%, p < 0.05). Anhedonia belongs to the mid frequent symptoms in all the three groups, the presence of comorbidities do not influence its frequency. Regarding vegetative symptoms (weight loss, weight gain, insomnia, hypersomnia, psychomotor agitation, psychomotor retardation and fatigue), sleeping problems and psychomotor retardation are significantly more frequent in the anxiety group (62.3%, 17.9%, 42 %, p < 0.01), psychomotor agitation is significantly more frequent in the disruptive grup (47.1% p< 0.01). During the study of cognitive symptoms (wothlessness, guilt and impairment decision making, suicid symptoms) concentration problem is present with the same frequency in all groups, and in the clear MDD and in the disruptive groups it is the second most frequent symptom. Among suicidal symptoms, thoughts of death are more

frequent in the anxiety (64.2%, $p < 0.01$) and in the disruptive groups than in the clear MDD group, and this symptom is the fourth most frequent in the anxiety and disruptive groups. Suicidal ideation is significantly the most frequent in the anxiety group (43.6%, $p < 0.05$). Comorbidities increase frequency of all the suicidal symptoms. Worthlessness is the most frequent in the disruptive group, and in this group it is the third most frequent symptom.

Table 6. Frequency of major depression symptoms in the three groups

Major Depressive Symptoms	**ClearMDD N=297**	**MDD+Anxiety N=212**	**MDD+Disruptive N=140**
Depressed Mood	60.9	67.5**	56.4
Irritability	69	73.6	80.7*
Anhedonia	41.1	47.2	35
Weight Loss	25.9	30.3	22.9
Weight Gain	17.5	15.1	10
Insomnia	52.4	62.3**	39.3
Hypersomnia	11.4	17.9**	6.4
Psychomotor Agitation	39.7	42	47.1**
Psychomotor Retardation	36.8	42**	23.6
Fatigue	58.2	65.1	53.6
Worthlessness	45.6	62.7	66.4**
Guilt	24.9	39.6**	29.3
Imp. Decision Making	65.3	66.5	67.4
Thoughts of Death	45.9	64.2**	60.7
Suicidal Ideation	33	43.6*	35

* $p < 0,05$, ** $p < 0,01$

4.2.3. Gender Differences Based on the Frequency of Depressive Symptoms in the Three Groups

In the clear MDD group psychomotor agitation (47.4%, $p < 0.01$), guilt (30.8%, $p < 0.05$) and impairment decision making (70.5%, $p < 0.05$) is significantly more frequent in case of boys, at the same time thoughts of death (52.9% $p < 0.05$) in case of girls. In the disruptive group, from the symptoms of criteria, the girls produce depressed mood (76.9%, $p < 0.05$) and anhedonia (53.8%, $p < 0.05$) more frequently than boys in the same group.

Table 7. Gender differences in relation to major depression symptoms in the three groups

	Clear MDD		MDD+Anxiety		MDD+Disruptive	
Major depressive symptoms	**Boys N=156**	**Girls N=141**	**Boys N=96**	**Girls N=116**	**Boys N=114**	**Girls N=26**
Depressed mood	60,9	61	60,4	73,3	51,8	76,9*
Irritability	71,2	66,7	75	72,4	78,9	88,5
Anhedonia	39,1	43,3	37,5	55,2	30,7	53,8*
Significant weight loss	24,4	27,7	28,1	32,2	21,9	26,9
Significant weight gain	14,4	21,3	15,6	14,7	11,4	3,8
Insomnia	50,6	54,3	55,2	68,1	37,7	46,2
Hypersomnia	9	14,2	12,5	22,4	6,1	7,7
Psychomotor agitation	47,4**	31,2	46,9	37,9	46,5	50
Psychomotor retardation	37,8	35,7	30,2	51,7	21,1	34,6
Fatigue	60,9	55,3	59,4	69,8	51,8	61,5
Worthlessness	47,4	43,6	60,4	64,7	64,9	73,1
Guilt	30,8*	18,4	37,5	41,4	28,1	34,6
Imp. Decision Making	70,5*	59,6	67,7	65,5	65,8	75
Thoughts of Death	39,7	52,9*	63,5	64,7	58,8	69,2
Suicidal ideation	28,2	38,3	43,8	43,5	34,2	38,5

** $p < 0,01$, *$p < 0,05$ (Chi square test)

4.3. Study of the Influence of Depressive Symptoms and Stressful Life Events on the Quality of Life of Schoolchildren *(community sample)*

4.3.1. Quality of Life and Clinical Level Depression

The mean scores of each quality of life summarized in Table 8. Statistically significant gender differences were found in case of two domains of quality of life, namely the domain of school satisfaction (girls =1.98, boys =2.09, $p< 0.001$, girls are more satisfied) and global quality of life (girls=1.66, boys =1.60, SD=0.71; $p< 0.035$, here the boys are more satisfied). Using the results from the short-version CDI, we looked at the probability of clinical depression for those over the 7-point threshold. In our sample, 388 pupils (14.8%) fell in this category (i.e clinical depressed). In the clinical depressed sample, the proportion of girls was higher than that of boys ($p<0.008$).

Table 8. Mean scores for different domains of the quality of life and depression in the whole sample, separated by genders

Quality of life/	**TOTAL**	**Girls**	**Boys**	**p**
CDI-S	**N=2620**	**N=1460**	**N=1160**	
****Total score (QoL28)**	22.81	22.81	22.81	
***School**	2.03	1.98	2.09	0.001
***Family**	1.36	1.36	1.35	
***Peer relations**	1.59	1.56	1.62	
***Alone-activity**	2.08	2.11	2.04	
***Physical health**	1.56	1.56	1.5	
***Mental health**	1.92	1.66	1.6	
***Global**	1.63	1.66	1.6	0.035
CDI-S<7	2232 (85.2%)	1220 (83.6%)	1012 (87.3%)	
CDI-S>=7	388 (14.8%)	240 (16.4%)	148 (12.7%)	0.008

Chi-square test

****Total quality of life score (QoL28): *higher* score denotes better quality of life.***Individual domains: *lower* score denotes better quality of life (see text before).

4.3.2. Stressful Life Events and Clinical Level Depression

In the clinically depressed group, significantly more children experienced 4 or more stressful life events (32.5%) than in the "non-depressed" group (21.9%) ($p < 0.0001$). Similar differences could be observed for girls: 34.2% of clinically depressed girls experienced 4 or more stressful life events; while only 21.9% of those girls who gave an account of fewer depressive symptoms had lived through 4 or more life events ($p<0.0001$). In contrast, for boys there was no significant difference between clinically depressed and non-depressed boys who experienced 4 or more life events.

Table 9. The relationship between stressful life events and depression for the whole sample (numbers of children in each category, percentages)

CDI-S score	**0-1 life event**	**2-3 life events**	**4 or more life events**	**TOTAL**
CDI-S<7	861 (38.6%)	882 (39.5%)	489 (21.9%)	2232 (100%)
CDI-S >=7	119 (30.7%)	143 (36.9%)	126 (32.5%)*	388 (100%)
TOTAL	980 (37.4%)	1025 (39.1%)	615 (23.5%)	2620 (100%)

*p = 0.0001, Chi-square test

4.3.3. Relationship between Quality of Life and Stressful Life Events

In the whole sample, the number of life events and gender of the child do not show significant interaction (p=0.176); that is, the difference between the boys' and girls' quality of life does not depend on the number of experienced stressful life events. There is no gender difference (p=0.789), so this refers to all three of the 'life-events' groups. A significant difference between stressful life events groups (p<0.0001) was found in the whole group (see in Table 10). All domains of quality of life a significantly decreasing QoL trend is associated with an increase in the number of stressful life events. The exception is the domain of alone-activity; this is the only QoL domain which seems not to be influenced by an increase in the number of life events. We found gender differences in cases of school satisfaction, peer relations and global life satisfaction. The data in the table 10 show that the girls consider their quality of life in the domain of school satisfaction better than boys do, while the boys are more satisfied with their global quality of life. In case of the domains of school satisfaction and global quality of life, there are also significant gender and life-events group differences; therefore, this difference relates to all three life-events groups, both for the whole sample and separately for the girls and boys. When examining, peer relations, it is clear that the number of life events and gender are linked. In the case of significant interaction (p = 0.011). In the domain of alone-activity, there are no significant differences.

Table 10. Relationship between the quality of life (QoL) and the number of stressful life events in the whole sample, separated

	Quality of Life							
Stressful life events	**Total**	**School**	**Family**	**Peer relation**	**Alone activity**	**Physical health**	**Mental health**	**Global**
0-1	23. 27	1.97	1.29	1.53	2.04	1.51	1.81	1.53
Girls	23. 41	1.90	1.28	1.47	2.07	1.50	1.78	1.55
Boys	23.11	2.04	1.30	1.61	2.02	1.52	1.84	1.51
2-3	22. 98	1.99	1.33	1.57	2.06	1.53	1.88	1.61
Girls	22. 87	1.97	1.34	1.59	2.12	1.52	1.90	1.64
Boys	23. 12	2.01	1.31	1.54	1.99	1.53	1.86	1.58
4/more	21. 78	2.20	1.51	1.70	2.16	1.68	2.12	1.83
Girls	21. 81	2.12	1.51	1.65	2.16	1.71	2.13	1.87
Boys	21.75	2.30	1.51	1.76	2.15	1.63	2.10	1.78
Groups	0.0001	0.0001	0.0001	0.0001	0.109	0.0001	0.0001	0.0001
Gender	0.789	0.0001	0.904	0.026	0.148	0.542	0.883	0.039
Inter-actions	0.176	0.198	0.604	0.011	0.577	0.320	0.396	0.762

The table shows the mean quality of life scores.

Total quality of life score (QoL28): *higher* score denotes better quality of life. Individual domains: *lower* score denotes better quality of life (see textbefore).

4.3.4. Relationship between Quality of Life and Depressive Symptoms

The results are shown in Table 11. The last three rows of the table show p-values of the two-way ANOVA analysis. It shows that members of the clinically depressed group are less satisfied with their total score for quality of life (QoL28) than are the members of the non-depressed group, and this is true for all QoL domains ($p<0.0001$). The examination of gender differences shows that, depressive symptoms more strongly related to school satisfaction for boys than for girls ($p=0.051$); also boys' depressive symptoms more strongly worsen the satisfaction with peer relations than in the case of girls ($p=0.025$). In the case of the quality of life total score (QoL28), there are gender differences in the depressed and non-depressed groups ($p=0.008$). Though the difference is significant in both groups, in the case of boys the difference between depressed and non-depressed groups is less remarkable than it is for girls. We found the same pattern for satisfaction with mental health. In the case of the evaluation of the global quality of life, there are significant differences both between groups and between genders, but as the interaction is also significant, additional examinations were necessary in the cases of gender and depressed groups. Results show that depressive symptoms significantly damage the global quality of life, and this effect is stronger for girls.

Table 11. The relationship between quality of life and the depression score for the whole sample, separated by gender

	Quality of Life							
CDI-S	**Total**	**School**	**Family**	**Peer relation**	**Alone activity**	**Physical health**	**Mental health**	**Global**
Cut off< 7	23. 35	1.96	1.28	1.51	2.05	1.49	1.77	1.53
Girl	23. 48	1.89	1.27	1.48	2.08	1.48	1.74	1.53
Boys	23. 20	1.29	1.29	1.55	2.02	1.51	1.81	1.54
Cut off≥7	19. 67	2.43	1.81	2.00	2.23	1.92	2.71	2.21
Girls	19. 43	2.42	1.82	1.95	2.26	1.97	2.80	2.34
Boys	20. 06	2.45	1.79	2.07	2.17	1.84	2.57	2.00
Groups	0.0001	0.0001	0.0001	0.0001	0.007	0.0001	0.0001	0.0001
Gender	0.303	0.051	0.951	0.025	0.222	0.223	0.097	0.0001
Interactions	0.008	0.187	0.547	0.574	0.840	0.058	0.002	0.0001

Two-way ANOVA. The table shows the mean quality of life scores.

Total quality of life score (QoL28): *higher* score denotes better quality of life. Individual domains:*lower* score denotes better quality of life (see text). The table shows the mean quality of life scores.

4.3.5. Variables Influencing the Quality of Life

4.3.5.1. Linear regression model

Table 12 shows the model. The CDI depression score is the factor which influences the quality of life the most strongly: the higher depression score goes together with a lower quality of life. The effects of other variables apart from the depression score are much weaker. The quality of life worsens with the increase of the number of stressful life events experienced and with increased age of the child. In our sample, the girls' subjective quality of life is better than that of the boys. We examined the interaction of stressful life events and the depression score, but the p-value of the interaction was not significant; that is, the presence of both variables does not influence the quality of life more strongly than in case of looking at each separately.

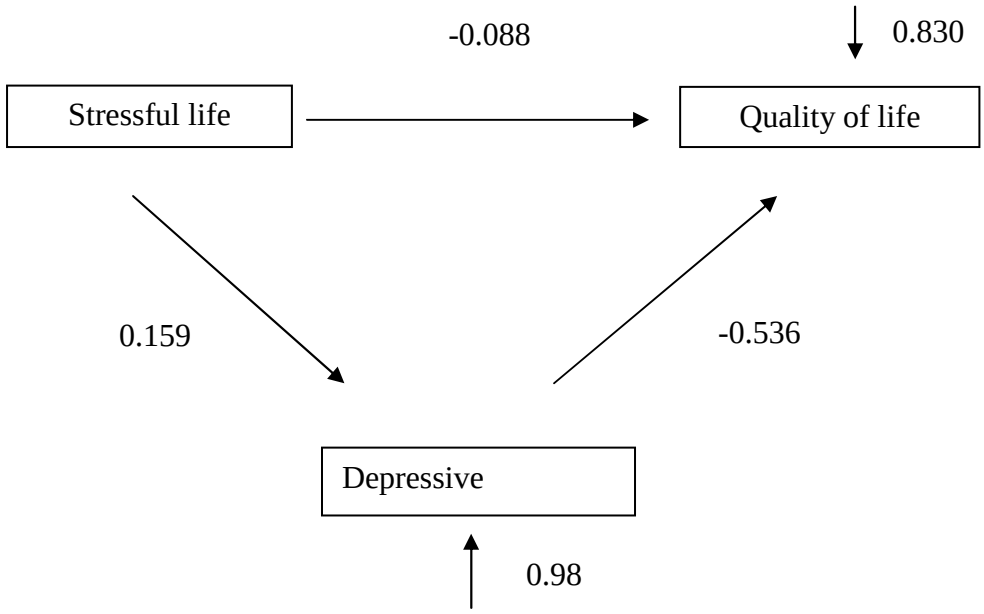
Table 12. The effect of depressive symptoms, stressful life events, gender, and age on the quality of life

	Coefficient	**p – values**	**95% confidence interval**	
			Lower	**Upper**
CDI-S score	-0.511	<0.001	-0.550	-0.352
No. of stressful life events	-0.058	0.039	-0.173	-0.041
Age	-0.035	0.033	-0.084	-0.042
Gender	0.034	0.036	0.002	0.041
[No. Stressful life events] X [CDI-S score]	-0.043	0.246	-0.426	-0.023

4.3.5.2. Clinical Level Depression and Stressful Life Events Effect on the Quality of Life

The results of path-analysis based on the evaluation of children of their own quality of life are shown in Figure 1.

Figure 1. The effect of depressive symptoms and stressful life events on the quality of life (The standardised regression Beta coefficients show the associations among variables.)



Stressful life events influence the quality of life: strength of effect r = - 0.088 (direct effect). On the other hand, it is noticeable that stressful life events also affect the quality of life through the depressive symptoms (indirect effect). The stressful life events (through the depression) on the quality of life can be calculated by multiplying the two numbers on the arrows: 0.159 * - 0.536 = - 0.085. The total of the direct and indirect effects precisely correspond with the correlation between stressful life events and the quality of life: r = - 0.173. All the effects of stressful life events on the quality of life (which are derived by correlation) were divided into direct and indirect parts. Though the value of the correlation coefficient is low, and the linear relationship is weak, it shows that on the basis of the self-evaluation by children, effects of stressful life events on the quality of life are expressed partly directly and partly indirectly through depressive symptoms.

5. DISCUSSION

In this study we examined the depressive symptoms and quality of life of 7-14-year-old children and adolescents in relation to several factors, like age, gender, comorbidities, and stressful life events. Depressive symptoms are examined with the help of a clinical sample take in two timeperiod (we examined the data of 559 and 649 depressed children, the latter was divided into three groups according to comorbidities: clear depression group, anxiety group and disruptive group), while quality of life was studied with the help of community sample (2620 schoolchildren).

5.1. Study of Depressive Symptoms in Relation to Age, Comorbidities and Gender

All the DSM-IV major depression symptoms were present in the samples, through the whole age span, and it corresponds to Carlson and Kashani's (1988) former results and those of Roberts and colleagues (1995). While controlling for sex and the inter-correlation between symptoms, the frequency of six symptoms increased together with age (depressed mood, hypersomnia, psychomotor retardation, fatigue, thoughts of death and suicidal ideations), at the same time frequency of one symptom decreased (psychomotor agitation). The influence of comorbidities had a great significance in case of depressed children because of its occurrence; it was present in 54.2% in the sample, which is consistent with the results of several former researches (Kovács et al. 1989, Birmaher et al. 1996). Anxiety was present in 32.6% and disruptive comorbidity in 21.6% in our sample. Anxiety comorbidities increased the occurrence of seven depressive symptoms (depressed mood, insomnia, hypersomnia, psychomotor retardation, guilt, thoughts of death and suicidal ideation), at the same time disruptive comorbidities increased the frequency of three depressive symptoms (irritability, psychomotor agitation and the worthlessness). Several former researches showed gender differences in the occurrence of depressive symptoms (Silverstein 1999, Williamson et al. 2000, Yorbik et al.2004, and Bongers 2003, Gaub and Carlson 1997), while other researches did not find these differences (Mitchell et al. 1988, Roberts et al.1995, Santalahti et al. 2005, Ryan et al.1987). Our results show gender differences in connection with the symptoms, while controlling for age and inter-correlation between symptoms of anhedonia, insomnia and hypersomnia are more frequent in case of girls, and psychomotor agitation is more frequent in case of depressed boys. The study of the influence of comorbidities showed that gender differences were present especially in the clear depressed group (psychomotor agitation, guilt,

concentration and decision impairment, thought of death and suicidal attempts). Comorbidities decreased gender differences in the frequency of symptoms (in case of anxiety comorbidity only suicidal attempts were more frequent and in case of disruptive comorbidities depressed mood and anhedonia were more frequent, in case of girls). Studying certain symptoms, among the criteria symptoms the frequency of depressed mood increased together with age, which is consistent with Carlson and Kashani's (1988) and Yorbik and colleagues' (2004) conclusions that depressed mood becomes more frequent with age, while irritability as the equivalent symptom of depressed mood (DSM-IV criteria) is most frequently present across all ages in our sample. All these suggest that in case of younger children the presence of irritability is expected to be more frequent as criterion, at the same time among adolescents major depression is more similar to that of the adults. With regard to age effects, our findings are not entirely consistent with the *DSM-IV* criteria according to which irritability can substitute for depressed mood as a required symptom in childhood. Specifically, depressed mood and irritability were relatively frequent across all ages, with more than 60% (depressed mood) and 70% (irritability) of patients displaying the 2 symptoms. In contrast, anhedonia was relatively infrequent across all age groups with rates generally below 50%. This suggests that anhedonia, not depressed mood, is the least frequent criterion symptom in depression among children and adolescents while irritability is significantly more common, occurring often in conjunction with, rather than as a substitute for depressed mood. It is supported by the fact that anxiety comorbidities increase the frequency of depressed mood; on the other hand, none of the comorbidities had any influence on the frequency of irritability and anhedonia. Irritability is the most frequent symptom in all the three groups, and anhedonia belongs to symptoms of average frequency.This also means that irritability is the criteria symptom which in younger ages contributes the mostly to the diagnosis of major depression among the criteria symptoms. The anhedonia is a stabile symptom in this age group and we could expect that with aging and with the cognitive development the ability of expressing emotions also develops, so the incidence of this symptom should also increase, but in spite of these facts this remains only a symptom with middle frequency.

In regard to sex differences, while controlling for age effects and symptom inter-correlation, we found that girls had significantly higher rates of anhedonia, and in case of disruptive comorbidity girls have the symptoms of depressed mood and anhedonia with higher frequency than boys. It means that it is more difficult to recognise the depression of boys with disruptive comorbidity, as their criterion is surely irritability, the identification of which is difficult among the disruptive symptoms. Among cognitive symptoms thoughts of death and

suicidal ideation also increased with age, their occurrence is increased by comorbidities, whether anxiety or disruptive, and in these groups they belong to the most frequent symptoms. It is consistent with the results of some earlier researches (Cooper and Goodyer 1996, Yorbik et al. 2004). It calls our attention to the importance of accurate and complete diagnoses, as the second reason of death in this age group is suicidal behaviour (Birmaher et al. 1996). An interesting result is that worthlessness the most often occurs in case of children with disruptive comorbidity, and in this group it is the third most frequent symptom. It may be related to the constantly present negative qualification from the side of the environment in connection with disruptive disorders. The symptom of impairment decision making is worth examining, as its occurrence does not depend on comorbidities, and in all the three groups it is one of the most frequent symptoms, although in the disruptive group the most frequent one is ADHD, the most important symptom of which is concentration and attention problem.

One could expect that in disruptive group this symptom should be more frequent compared to the other two, but during the diagnostic process the impaired decision making symptom can be regarded as a depressive symptom in ADHD only if it became more serious during the depressed mood or irritability. This makes it possible for us to evaluate correctly this symptom in relation to its frequency.

On the basis of all these we can state that attention problems in connection with depression are not damaged further by disruptive comorbidities, and that concentration impairments appearing in school performance are noteworthy to major depression. Gender differences in case of cognitive symptoms occur in cases without comorbidities (guilt, impairment decision making, and thoughts of death and suicidal attempts in case of girls). We can state that comorbidities reduce gender differences during the appearance of the symptoms. We found that several vegetative symptoms increased with age, including hypersomnia, psychomotor retardation and fatigue, which partly corresponds to the results of some previous studies (Ryan 1987, Mitchell 1988, Yorbik 2004), and psychomotor agitation were the only symptoms that diminished with age. In case of anxiety comorbidities insomnia, hypersomnia and psychomotor retardation is also more frequent, as well as the disruptive comorbidity increases the frequency of psychomotor agitation, which is not surprising, as the most frequent comorbidity was ADHD in our sample. Given that depression and ADHD share the symptom of psychomotor agitation and that there is a developmental trend in ADHD diagnostic rates (Willoughby et al.2003), we examined whether the reduction in psychomotor agitation observed in depression in older children was due to age-related drops in ADHD comorbidity. We found that psychomotor agitation symptoms decreased significantly across

age groups, even among children without comorbid ADHD, suggesting that this reduction is a component of the changing neurovegetative profile during adolescence rather than a by-product of decreased rates of comorbid ADHD in adolescents. In case of girls sleeping problems are more frequent, while in case of boys it was psychomotor agitation, and this general difference will disappear in the presence of comorbidities. Several studies have found connection between somatic symptoms and childhood and adolescence depression (McGrath et al. 1983, Garber et al. 1990, Campo et al. 1994). Somatic complaints are the symptoms of many anxiety disorders, on the basis of DSM-IV. However, whereas we found that somatic complaints were present in average 37% across all age groups of our sample. We did not find any age trends in the rate of somatic complaints in this sample. Notably, this lack of age effects was not due to age differences in comorbid anxiety disorders. Therefore, somatic complaints appear to be a common symptom in both depressed children and adolescents; overall, it was reported at a higher rate than 4 depression symptoms, namely, weight loss, weight gain, hypersomnia, and guilt. It was more frequent in case of girls. Thus, somatic complaints should be considered an associated feature of the symptom profile of MDD in pediatric populations.

Tabla 13. The examinined parameters effect on the depressive symptoms

	Depressed Mood	Irritability	Anhedonia	Weight Loss	Weight Gain	Insomnia	Hypersomnia	Psychomot Agit	Psychomot Ret	Fatigue	Worthlessness	Guilt	Imp Dec Making	Thoughts of Death	Suicidal Ideation	Somatic Compl.
Age	+						+	-	+	+				+	+	
Gender			**f**			**f**	**f**	**m**								**f**
Anxiety comorbidity	+					+	+		+			+		+	+	
Disruptív comorbidity		+						+			+					

+ = increase, - = decrease, m = male, f = female

5.2. Quality of Life, Stressful Life Events and Depressive Symptoms

The examination of the quality of life is a very important field of research, and in the last few years there has been increasing interest concerning the child and adolescent population. We examined the quality of life depressive symptoms and stressful life events in case of 2620 children in community sample. For the whole of our sample, the average quality of life of

these schoolchildren was satisfactory (22.81 points). According to our research the total score of the quality of life (QoL28) was 19.67 in the case of children with clinical depression, while in the group of children with less depressive symptoms it was 23.35. Thus, depressive symptoms worsened the quality of life in our sample, which is consistent with the literature (Kopp and Kovacs 2006, Sawyer et al.2002, Bastiaansen et al. 2004, Munoz et al. 2005, Clark and Kirisci 1996). The mean of experienced stressful life events was 2.35, and the members of the clinically depressed group of pupils experienced significantly more life events than those with few depressive symptoms. We have found some characteristic gender differences in our sample. In the whole sample, 14.8% of the pupils had clinical depression on the basis of Short Version of CDI. Two-thirds of the depressed children were girls, and one-third boys. These data are consistent with the data reported in the Hungarian and international literature (Vetró et al. 2003, Birmaher et al. 1996). Comparing the individual domains of the quality of life, there were gender differences in two cases: girls were more satisfied with the school experience, while boys considered the global quality of life more highly. The girls experienced significantly more life events than the boys. In the clinically depressed group, girls lived through significantly more life events than the boys. These findings are also consistent with the literature (Vetró et al.1997, Williamson et al. 1998)

On the basis of our results, an increase in the number of stressful life events worsened the quality of life, in the whole sample and also in both genders. In the evaluation of individual domains, and comparison of boys and girls, only the domain of alone activity differed from this overall finding. A major decrease could be found in the quality of school life for boys as the effect of stressful life events, while this decrease could be found in the global quality of life and quality of peer-relations in girls. Considering the above-mentioned facts, we can suppose that school achievement and satisfaction with school is less important for girls, while the skills of individual initiative and peer relations are more influenced by the number of experienced stressful life events. These are the domains that have more sensitive reactions. Or alternatively, boys are probably more sensitive in reporting the changes in achievement.

Considering the different domains of quality of life, children with clinical level depression had lower qualities of life in all 7 domains, than the group of children with few depressive symptoms. Girls without clinical depresson disorder rated their qualities of life higher than boys. In contrast, girls with clinical depression evaluated their quality of life as lower than did depressive boys. Consequently, it seems that depression has more negative effects on the quality of life for girls than it does for boys. Depressive symptoms led to a greater decrease in quality of school life in boys, and in quality of peer relations in boys. Thus in the case of

clinical depression, boys are more sensitive to their school achievements, and these are more sensitive to their quality of peer relations. According to the global domain, depressive girls tends to judge worse their quality of life.

Considering that life events, depressive symptoms and gender all have an effect on the quality of life, we examined these effects in a collective model. The model includes age, because of its relationship with depression and life events; namely that, according to the literature (Birmaher et al.1996), frequency of depression increases in adolescence, and that the number of life event increases with age. Our results show that depression has the most negative effect on the quality of life; in contrast, stressful life events, age and gender have relatively minor effects. Stressful life events influence the development of depression, and clinical depression lowers quality of life. But the question arises as to whether stressful life events have a direct effect or an indirect effect via depression on the quality of life. According to the self-assessment of children, stressful life events worsen the quality of life both directly (50%), and indirectly through depressive symptoms (50%). Overall, from the children's point of view, depressive symptoms are reported to have more negative effects on the quality of life than do stressful life events.

5.3. Conclusions

In conclusion, using a large clinical sample of depressed children and adolescents from Hungary, we observed significant developmental differences in the presentation of depression. We used age as a continuous variable, and we used semi-structured interviews during examining clinical samples.

1) We hypothesized that there are some developmental differences in depressive symptom presentation. Six symptoms increased with age depressed mood, hypersomnia, psychomotor retardation, fatigue, thoughs of death, suicidal ideation, and the frequency of psychomotor agitation decreased with age. We also observed stable and elevated rates of irritability, which were concurrent with stable and low rates of anhedonia across all age groups. Irritability is the most frequent symptom. The above results points out the importance of irritability in case of younger children.
2) We hypothesized that there are gender differences in the occurrence of psychopathological symptoms. Anhedonia, insomnia and hypersomnia are more frequent in case of girls, and psychomotor agitation is that in case of boys.
3) We hypothesized that somatic symptoms are more frequent in younger age. This hypothesis of ours have not been proved, therefore, somatic complaints appear to be

a common symptom in both depressed children and adolescents; overall, it was reported at a higher rate than 4 depression symptoms, namely, weight loss, weight gain, hypersomnia, and guilt, it was more frequent among girls. Thus, somatic complaints should be considered an associated feature of the symptom profile of MDD in pediatric populations.

4) We hypothesized that the frequency of depressive symptoms is increased by comorbidities. Anxiety comorbidities have increased the occurance of most depressive symptoms (depressed mood, insomnia, hypersomnia, psychomotor retardation, guilt and thought of death, suicidal ideation), while in case of disruptive comorbidities the presence of irritability, psychomotor agitation, worthlessness is striking. In case of boys irritability may be expected as a compulsory symptom.
5) We hypothesized that stressful life events damage the quality of life, and it is aggravated by depression. Stressful life events worsen the quality of life both directly (50%), and indirectly through depressive symptoms (50%). Overall, from the children's point of view, depressive symptoms are reported to have more negative effects on the quality of life than do stressful life events.

5.4. Limitations

Depressive study participants were selected for a genetic study of risk factors of childhood-onset depression, and our sample selection was biased toward families with 2 or more children. However, we only included 1 child from each family. A further limitation is that depressive symptoms were examined as present or absent. This approach could have obscured more nuanced age and sex effects regarding the severity (rather than rate) of specific symptoms. Our sample encompassed different sex distributions across age groups. In younger ages, we had significantly more boys than girls, while in older ages we had significantly more girls than boys. Although our ALR model adjusts for such age and sex differences simultaneously, we still have an imbalance in sex ratios at the youngest and oldest age groups. This could limit our power to detect subtle sex differences specific to those age periods. The community sample cannot be considered as a representative of the Hungarian population of schoolchildren as a whole. The study of depressive symptoms happened with CDI Short Version, the use of the complete version would have resulted in more detailed data that could have been compared to international literature more widely. About the children's life events only the parents gave us information. In case of interviewing the children the control of one-sided information would have been possible. We did not ask about the life event in the year

before the research, which may show closer connection to depressive symptoms. Our quality of life results were analyzed on the basis of children's self-assessments, and the factors we studied undoubtedly and considerably influenced the quality of life of this population of schoolchildren, but our results indicate that several further factors might also have an effect on the child's quality of life.

5.5. Important Findings and Clinical Implications

The diagnostical criteria of childhood and adolescence depression (DSM-IV) do not accommodate to the characteristics of time of life. It renders diagnosis more difficult, though we know that untreated major depression has severe, long-term consequences. Our results are

1. Among criteria, irritability is the most frequent symptom in childhood and in adolescence, and it contributes the most frequently to the diagnosis of major depression among the criteria symptoms in younger ages.

2. Somatic symptoms are more frequent among depressed children and adolescents than several other symptoms, thus as additional symptoms may contribute to successful diagnostic process in case of these age groups.

3. Comorbidities hamper the identification of depressed children, especially in case of boys with disruptive comorbidity, because from criteria symptoms irritability is more frequent compared to the other two criteria symptoms and it is difficult to recognise among the disruptive symptoms, and the worthlessness may call attention to depression. The concentration problems, that often appear in problems with academic performance may be the sign of major depression.

4. Depressive symptoms have the most negative effect on the quality of life. Stressful life events worsen the quality of life both directly (50%), and indirectly through depressive symptoms (50%). This fact strengthens the importance of the statements above. Considering age is essential to early diagnosis and early onset therapy.

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APPENDIX

Age and Sex Analyses of Somatic Complaints and Symptom Presentation of Childhood Depression in a Hungarian Clinical Sample

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Objective: To determine whether the symptom presentation of major depressive disorder (MDD) in a large clinical sample of youngsters is influenced by age, sex, and the interaction of age and sex.

Method: The sample included 559 children (mean age = 11.69 years; range, 7–14 years; 247 girls) with MDD recruited from 23 mental health facilities across Hungary. Psychiatric evaluations were conducted via the semistructured Interview Schedule for Children and Adolescents-Diagnostic Version (ISCA-D). Final *DSM-IV* diagnoses were rendered via the best-estimate diagnostic procedure. Evaluations were conducted between April 2000 and May 2005.

Results: Six depression symptoms increased with age: depressed mood (odds ratio [OR] = 1.10, $P < .05$), hypersomnia (OR = 1.17, $P < .05$), psychomotor retardation (OR = 1.11, $P < .05$), fatigue (OR = 1.13, $P < .01$), thoughts of death (OR = 1.11, $P < .05$), and suicidal ideation (OR = 1.18, $P < .01$), while psychomotor agitation decreased with age (OR = 0.91, $P < .05$). Boys were less likely to evidence anhedonia (OR = 0.67, $P < .05$), insomnia (OR = 0.68, $P < .05$), and hypersomnia (OR = 0.56, $P < .05$) but more likely to have psychomotor agitation (OR = 1.59, $P < .01$). There were no age-by-sex interactions. Rates of somatic complaints did not decrease with age (OR = 1.01, $P > .05$).

Conclusions: The symptom presentation of MDD becomes somewhat more neurovegetative as children get older. However, girls display more affective and atypical symptoms across all age groups. Somatic complaints were common regardless of age and should be considered an associated feature of depression in children and adolescents.

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Over the past 3 decades, a large body of research has shown that children and adolescents can meet diagnostic criteria for major depressive disorder (MDD) as defined in standard diagnostic manuals (eg, *DSM-IV*; see review by Birmaher et al[1]). However, questions have remained about the appropriateness of such criteria for younger age groups. Most questions concern 2 issues, namely, (1) Are *DSM* criteria for MDD able to accommodate age-related differences in the likelihood of particular symptoms? and (2) Are there different symptoms associated with MDD as a function of a child's age, sex, and age-by-sex interactions? Surprisingly, research on age and sex differences in depressive symptomatology with clinical populations is scarce, and our current understanding of these effects is mostly based on studies using small sample sizes that limit the identification of subtle effects.

A small number of studies have examined developmental differences in rates of specific symptoms across depressed children and adolescents. For example, Ryan et al[2] reported that, compared to depressed children, adolescents with MDD were more likely to display hopelessness, hypersomnia, and weight gain/loss and less likely to display somatic complaints and psychomotor agitation. In a similar study, Yorbik et al[3] found that depressed adolescents displayed significantly higher rates of hopelessness/helplessness, fatigue, lack of energy/tiredness, hypersomnia, weight loss, and suicidality than depressed children. However, Mitchell et al[4] found hypersomnia to be the only symptom more frequent in clinically depressed adolescents than in depressed children. Discrepant findings may be related to significant methodological differences between the studies. For example, Mitchell and colleagues'[4] study was conducted with a small sample of inpatient youth, while the studies by Ryan et al[2] and Yorbik et al[3] had larger samples of outpatient children and adolescents.

Given that somatic symptoms have been historically viewed as a common presentation of childhood depression,[5] several studies have examined the association between somatic complaints and depression in younger ages,[4,6] but they have yielded contradictory findings. For example, some researchers reported more somatic complaints among

prepubertal children compared to postpubertal children,[2] while others failed to find this developmental difference.[4] Such discrepant findings may reflect that none of these studies have controlled for comorbid anxiety that could have affected the results given the high rates of anxiety disorders among depressed youths (eg, Kovacs[7]) and the strong association between somatic symptoms and anxiety in childhood.[8]

All in all, extant studies of age-related differences in symptom presentation among clinically depressed pediatric samples suggest that adolescents tend to have more vegetative symptoms than children, yet there is no clear picture regarding differences in specific symptoms during various ages. Furthermore, previous examinations of age differences have used pubertal status (prepubertal versus postpubertal) to subdivide the samples. Examining chronological, age-related changes in symptom presentation continuously, rather than categorically, may reveal more subtle developmental effects on symptom presentation throughout middle childhood and adolescence.

Examinations of sex differences in child and adolescent depression have generally focused on rates of diagnosis and severity of symptoms,[9,10] with only a few studies of rates of specific symptoms. For example, Mitchell et al[4] found no sex differences in rates of various depressive symptoms in a small sample of inpatient children and adolescents with MDD. Similarly, Roberts et al[11] failed to find sex differences in symptom presentation in a small community-based sample of adolescents meeting criteria for major depression. However, studies with larger samples have reported sex differences in appetite and weight fluctuations. For example, Williamson et al[12] found higher rates of weight gain among depressed girls compared to boys. Similarly, Yorbik et al[3] reported that girls with MDD had higher rates of increased appetite than boys, but this effect was only observed among adolescents. Ryan et al,[2] however, failed to find sex differences in weight gain or appetite changes, although they found that preadolescent boys experienced more fatigue symptoms than preadolescent girls. These inconsistent findings may be due to significant differences in sample sizes and possible cohort effects, as studies differed greatly in the decade of data collection.

Therefore, in the present study, we sought to further our understanding of developmental changes in the symptomatology of childhood-onset depression using a uniquely large clinical sample of depressed children and adolescents in Hungary. Our first aim was to examine developmental differences in depressive symptom presentation using age as a continuous variable. Our second aim was to examine sex differences, as well as sex-by-age effects, in symptomatology. In addition to depressive symptoms, we also assessed age and sex differences in the presence of somatic complaints, given the reported high rates of somatic symptoms among depressed children.[6,13] Further, given that there is overlap in some symptoms between depression and other disorders (eg, anxiety, attention-deficit/hyperactivity disorder [ADHD]), we examined the effect of comorbid diagnoses on 2 symptoms: somatic complaints, and psychomotor agitation. Finally, our large sample allows us to use an advanced statistical method such as Alternating Logistic Regression (ALR),[14] which is uniquely suited for simultaneously modeling multiple outcomes (eg, symptoms) while controlling for the possible intercorrelation between these outcomes.

METHOD

Participants

The sample included 559 children (247 girls) who were enrolled in a study of genetic and psychosocial risk factors for childhood-onset depression between April 2000 and May 2005. The mean age at evaluation was 11.69 years (SD = 2.00 years). Ethnic composition was representative of the ethnic composition of Hungary: 93.9% white, 3.6% gypsy (Roma), 2.3% multiracial, and 0.2% African. Subjects were recruited from 23 mental health facilities across Hungary. Children presenting at each site were selected for further assessment if they met the following criteria: 7.0 to 14.9 years old, no evidence of mental retardation, no evidence of major systemic medical disorder, availability of at least 1 biologic parent, and a 7–14.9-year-old sibling (required by the study's genetic component). Siblings are not included in this article.

Measures and Procedures

Enrollment and assessment procedures have been described in detail in previous publications.[15,16] Children were screened for depressive symptoms by self-report and parental questionnaires. Those who scored above clinically established cutoffs received psychiatric interviews on 2 independent occasions administered by different trained psychiatrists/psychologists.

Clinical evaluations were conducted with the semistructured Interview Schedule for Children and Adolescents-Diagnostic Version (ISCA-D), an extension of the Interview Schedule for Children and Adolescents (ISCA).[17] Each clinician interviewed the parent and the child separately and rendered an overall severity rating for each symptom. Good interrater reliability for symptom ratings has been reported.[15,16] Final diagnoses were rendered by experienced psychiatrists using the best-estimate diagnostic procedure.[18] Only those meeting criteria for MDD at the time of the evaluation were included in the present analysis. We examined the presence or absence of 16 *DSM-IV* criterion symptoms from the ISCA-D (see Table 1). We used clinicians' overall ratings and dichotomized them as clinically significant (entered into a given diagnosis) versus subclinical or absent.

Statistical Analysis

To estimate the effect of age, sex, and age-by-sex interactions on symptom presentation, we used ALR[14] fitting a multivariate model of age and sex on the 16 symptoms of

Table 1. Unadjusted Rates (%) of Depressive Symptoms Across Age Groups in Children With Major Depressive Disorder

Symptom	Age at Interview, y								Statistic[a] (χ^2)
	7 (n = 16)	8 (n = 46)	9 (n = 70)	10 (n = 70)	11 (n = 91)	12 (n = 91)	13 (n = 92)	14 (n = 83)	
Depressed mood	63	61	66	69	73	60	73	81	5.04*
Irritability	75	76	80	83	86	79	73	81	NS
Anhedonia	38	43	49	40	43	48	51	43	NS
Weight loss	25	28	36	26	26	26	30	40	NS
Weight gain	6	28	21	26	26	16	24	14	NS
Insomnia	63	46	60	49	63	55	55	57	NS
Hypersomnia	13	11	6	10	11	14	17	23	9.33**
Psychomotor agitation	63	52	56	53	45	36	39	43	7.70**
Psychomotor retardation	31	30	34	29	37	46	39	47	6.49*
Fatigue	69	41	60	63	64	70	67	70	7.57**
Feelings of worthlessness	44	50	59	57	59	63	60	63	NS
Guilt	25	35	41	33	31	35	30	35	NS
Impaired decision-making	75	65	73	76	70	70	67	75	NS
Thoughts of death	44	35	59	61	55	68	55	65	6.69**
Suicidal ideation	25	17	34	39	41	44	45	49	13.87***
Somatic complaints	50	35	36	29	37	35	43	35	NS

[a]Mantel-Haenszel χ^2, df = 1.
*$P < .05$.
** $P < .01$.
*** $P < .001$.
Abbreviation: NS = not statistically significant at nominal $\alpha < .05$.

interest. ALR is a type of Generalized Estimating Equation (GEE) [19] that allowed us to simultaneously model the endorsement of each of the 16 symptoms while accounting for the possible intercorrelation of symptoms within participants. This method was initially created for analysis of intercorrelated cluster data[20] and has been extended to the analysis of intercorrelated outcomes.[21]

RESULTS

Unadjusted Rates of Specific Depressive Symptoms by Age and Sex

Table 1 presents the rates of endorsement of each symptom by age. Depressed mood, hypersomnia, psychomotor retardation, fatigue, thoughts of death, and suicidal ideation increased linearly with age. Psychomotor agitation was the only symptom that decreased linearly with age. Table 2 presents the rates of endorsement of each symptom by sex. Six symptoms were significantly more common in girls than boys, namely, depressed mood, anhedonia, insomnia, hypersomnia, psychomotor retardation, thoughts of death, and somatic complaints. In contrast, only psychomotor agitation was more commonly reported in boys than in girls.

Table 2. Unadjusted Rates (%) of Depressive Symptoms for Girls and Boys With Major Depressive Disorder

Symptom	Girls (n = 247)	Boys (n = 312)	Statistic[a] (χ^2)
Depressed mood	74.1	65.4	4.90*
Irritability	77.7	81.1	NS
Anhedonia	51.0	41.0	5.55*
Weight loss	32.8	28.2	NS
Weight gain	22.3	20.8	NS
Insomnia	61.1	51.6	5.08*
Hypersomnia	18.2	9.9	8.05**
Psychomotor agitation	38.5	51.6	9.59**
Psychomotor retardation	43.7	34.0	5.47*
Fatigue	65.6	62.8	NS
Feelings of worthlessness	61.1	57.1	NS
Guilt	33.2	34.3	NS
Impaired decision-making	67.2	74.4	NS
Thoughts of death	62.8	54.2	4.17*
Suicidal ideation	43.7	36.5	NS
Somatic complaints	42.1	32.1	6.01*

[a]Mantel-Haenszel χ^2, df = 1.
*$P < .05$.
**$P < .01$.
Abbreviation: NS = not statistically significant at nominal $\alpha < .05$.

Age and Sex Effects in Rates of Depressive Symptoms Adjusted for Intercorrelation Between Symptoms

Table 3 shows the adjusted odds ratio (AOR) of each symptom by sex and age while controlling for age, sex, and the correlation between symptoms. Results from the ALR indicated a significant effect of age ($\chi^2_{16} = 35.91$, $P = .003$) and sex ($\chi^2_{16} = 38.65$, $P = .001$). No age-by-sex interaction was observed, $\chi^2_{16} = 16.53$, $P = .42$. Consistent with the unadjusted results presented above and while controlling for sex and the intercorrelation between symptoms, the AOR of 6 symptoms increased with age, namely, depressed mood (10% increased odds per year), hypersomnia (17% increased odds per year), psychomotor retardation (11% increased odds per year), fatigue (13% increased odds per year), thoughts of death (11% increased odds per year), and suicidal ideation (18% increased odds per year). Only psychomotor agitation was more frequent in younger children (9% reduced odds per year). While controlling for age and intercorrelation between symptoms, being male significantly decreased the odds of 4 specific symptoms,

Table 3. Adjusted Multivariate Odds Ratios (95% CI) of Each Symptom Adjusted for Age and Sex via Alternating Logistic Regression[a]

	Between-Subject by Symptom Effects	
Symptom	Age: Per Year	Sex: Male
Depressed mood	1.10 (1.01–1.21)*	0.71 (0.49–1.03)
Irritability	0.98 (0.88–1.10)	1.22 (0.80–1.86)
Anhedonia	1.01 (0.93–1.10)	0.67 (0.48–0.95)*
Weight loss	1.06 (0.96–1.16)	0.84 (0.58–1.22)
Weight gain	0.94 (0.85–1.03)	0.87 (0.58–1.31)
Insomnia	1.00 (0.92–1.09)	0.68 (0.48, 0.96)*
Hypersomnia	1.17 (1.02–1.35)*	0.56 (0.34–0.93)*
Psychomotor agitation	0.91 (0.83–0.99)*	1.59 (1.12–2.24)**
Psychomotor retardation	1.11 (1.01–1.21)*	0.71 (0.50–1.01)
Fatigue	1.13 (1.03–1.23)**	0.97 (0.68–1.39)
Feelings of worthlessness	1.06 (0.97–1.15)	0.88 (0.62–1.25)
Guilt	0.99 (0.90–1.08)	1.04 (0.72–1.49)
Impaired decision-making	1.02 (0.93–1.12)	1.43 (0.99–2.08)
Thoughts of death	1.11 (1.02–1.22)*	0.76 (0.54–1.08)
Suicidal ideation	1.18 (1.08–1.29)**	0.86 (0.61–1.21)
Somatic complaints	1.01 (0.92–1.10)	0.65 (0.46–0.93)*

[a]No sex-by-age interactions were noted.
*$P < .05$.
**$P < .01$.

namely, anhedonia (33% reduced odds), insomnia (−32%), hypersomnia (−44%), and somatic complaints (−35%), and significantly increased the odds ratio of psychomotor agitation (59% increased odds).

Finally, given the historical interest in whether somatic complaints may be a presenting symptom in pediatric depression, we examined its rate among children without comorbid anxiety disorder (n = 398). The rate of somatic complaints in this group was 29% on average (range, 20%–46% across all ages), a rate higher than other depressive symptoms such as hypersomnia and weight gain. Consistent with our full sample analysis, no age effects on somatic complaints were noted among children without comorbid anxiety ($\chi^2_1 = 0.53$, $P = .47$). However, the sex difference in somatic symptoms in the full sample did not remain significant after controlling comorbid anxiety disorder (33% in girls vs 26% in boys), $\chi^2_1 = 1.77$, $P = .18$. We also examined the rate of psychomotor agitation in children without comorbid ADHD (n = 449). Consistent with our full sample analysis, we found an age effect on psychomotor agitation (decreasing rates of agitation in older cases) even among children without comorbid ADHD ($\chi^2_1 = 7.19$, $P < .01$). Finally, also consistent with our full sample analysis, boys were more likely than girls to present psychomotor agitation after controlling for comorbid ADHD ($\chi^2_1 = 10.13$, $P < .01$).

DISCUSSION

In this study, we examined age and sex differences in rates of depressive symptoms in a uniquely large sample of children and adolescents diagnosed with MDD. Our large sample allowed for the simultaneous assessment of age and sex effects using ALR, which controls for possible intercorrelations of symptoms within participants and provides robust, more reliable estimates than previously used methods. Our findings indicate significant sex and age differences in the presentation of several symptoms, but surprisingly, we did not find any age-by-sex interactions.

Consistent with previous studies,[2–4] we found that several neurovegetative symptoms increased with age, including hypersomnia, psychomotor retardation, and fatigue. This pattern was accompanied by a significant increase in depressed mood, thoughts of death, and suicidal ideation and a reduction in rates of psychomotor agitation. Our results are consistent with Weiss and Garber's[22] meta-analytic review in which they concluded that depression is not isomorphic in symptomatology or syndrome presentation throughout early development, despite some studies indicating that symptom presentation is relatively unchanged between children and adolescents (eg, Ryan et al[2]). Specifically, our results indicate that the presentation of depression becomes more neurovegetative as children transition from childhood into adolescence. Our findings are also consistent with Carlson and Kashani's[23] conclusions that depressed mood becomes more frequent with age. Yorbik et al[3] also found an increase in rates of depressed mood in adolescence compared to childhood.

With regard to age effects, our findings are not entirely consistent with the *DSM-IV* criteria according to which irritability can substitute for depressed mood as a required symptom[24] in childhood. Specifically, depressed mood and irritability were relatively frequent across all ages, with more than 60% of patients displaying the 2 symptoms. In contrast, anhedonia was relatively infrequent across all age groups with rates generally below 50%. This suggests that anhedonia, not depressed mood, is the least frequent core symptom in depression among children and adolescents while irritability is significantly more common, occurring often in conjunction with, rather than as a substitute for, depressed mood.

Given that depression and ADHD share the symptom of psychomotor agitation and that there is a developmental trend in ADHD diagnostic rates (see Willoughby),[25] we examined whether the reduction in psychomotor agitation observed in depression in older children was due to age-related drops in ADHD comorbidity. We found that psychomotor agitation symptoms decreased significantly across age groups, even among children without comorbid ADHD, suggesting that this reduction is a component of the changing neurovegetative profile during adolescence rather than a by-product of decreased rates of comorbid ADHD in adolescents.

However, whereas we found that somatic complaints were present in 30%–50% of our sample (average 37% across all age groups), we did not find any age trends in the rate of somatic complaints in this sample. Notably, this lack of age effects was not due to age differences in comorbid anxiety disorders. Therefore, somatic complaints appear to be a common symptom in both depressed children and

adolescents; overall, it was reported at a higher rate than 4 depression symptoms, namely, weight loss, weight gain, hypersomnia, and guilt. Thus, somatic complaints should be considered an associated feature of the symptom profile of MDD in pediatric populations.

In regard to sex differences, while controlling for age effects and symptom intercorrelation, we found that girls had significantly higher rates of anhedonia, insomnia, and hypersomnia and lower rates of psychomotor agitation. This suggests that girls tend to have a more affective (anhedonia) and atypical (hypersomnia) presentation of depression across all developmental periods. Previous studies have yielded inconsistent results with regard to sex differences and depression symptoms. For example, 2 studies found higher rates of eating-related symptoms (eg, weight gain and increased appetite) among girls compared to boys,[3,12] but this finding was not replicated in other studies,[2,4,11] albeit with smaller samples. Such discrepancies may be partially due to methodological differences between earlier and current studies. For example, Williamson et al[12] reported sex comparisons only on symptoms of atypical depression and did not include all symptoms we assessed (eg, anhedonia, insomnia). Furthermore, the previous large sample studies used patients diagnosed during the normal course of clinical admission at a large psychiatric hospital. Our study was instead conducted with a clinical research sample that underwent a more comprehensive and controlled assessment process (eg, duplicate psychiatric interviews, best-estimate consensus diagnoses). It is possible that this resulted in more reliable diagnoses in our sample and less heterogeneity in comorbid symptoms and diagnoses, which could otherwise mask some of the sex effects we detected. Finally, it is also possible that the sex effects we observed may be more specific to psychiatric samples of European youth.

Finally, we were surprised that we failed to find any age-by-sex interaction in symptom rates. Given our large sample and analytic technique, we are confident that we would have been able to identify subtle interaction effects had they been there. This nonfinding is noteworthy, given that sex differences in the rate of depression diagnoses emerge during adolescence and that these sex differences have been related to cognitive, social, and physiologic developmental changes.[10] However, our findings indicate that in clinically referred and psychiatrically-diagnosed depressed children and adolescents, sex differences in the symptomatology of depression are stable across developmental periods.

Limitations

Study participants were selected for a genetic study of risk factors of childhood-onset depression, and our sample selection was biased toward families with 2 or more children. In this article, however, we only included 1 child from each family. A further limitation is that depressive symptoms were examined as present or absent. This approach could have obscured more nuanced age and sex effects regarding the severity (rather than rate) of specific symptoms. Finally, our sample encompassed different sex distributions across age groups. In younger ages, we had significantly more boys than girls, while in older ages we had significantly more girls than boys. Although our ALR model adjusts for such age and sex differences simultaneously, we still have an imbalance in sex ratios at the youngest and oldest age groups. This could limit our power to detect subtle sex differences specific to those age periods.

In conclusion, using a large clinical sample of depressed children and adolescents from Hungary, we observed significant developmental differences in the presentation of depression. Specifically, we noted an increase in vegetative symptoms with age. We also observed stable and elevated rates of irritability, which were concurrent with stable and low rates of anhedonia across all age groups. While current *DSM-IV* criteria indicate that irritability may be a substitute for depressed mood as a required symptom, our findings indicate that anhedonia, not depressed mood, is the infrequent symptom in this age group. Therefore, irritability should also be considered a substitute for anhedonia in this population. Our findings also suggest significant sex differences in the presentation of depression, but these differences are stable across development. Finally, our results replicate and extend prior findings with a similar large, US-based clinical sample,[3] underscoring the transcultural similarity of MDD presentation in youngsters.

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Stressful Life Events in a Clinical Sample of Depressed Children in Hungary

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Abstract

Background—There is limited information on the characteristics of stressful life events in depressed pediatric clinical populations and the extent to which sex, age, and their interactions may influence the relations of life events and depression. Using a very large clinical sample of children and adolescents with major depressive disorder (MDD), we therefore examined life events in various ways as well as their relations to age and sex.

Method—The study included a clinic-based sample of 434 children (ages 7–14) with a DSM-IV diagnosis of MDD and their mothers, and a school-based comparison sample of 724 children and their mothers. Life event information was obtained from the mothers.

Results—Children with MDD had twice the number of lifetime stressful events than did the comparison group, with very high levels of stressors by the age of 7–9 that stabilized across adolescence. In contrast, the comparison sample experienced a gradual increase in stressful life events as a function of age up to mid-adolescence. Parental health events, death of close relatives, and intra-familial events were significantly associated with MDD diagnosis. There were significantly stronger associations between parental health- as well as death-event clusters and MDD diagnosis among younger children than adolescents.

Limitations—Geographical differences between the clinical and comparison samples, as well as possible parental reporting biases may affect the generalizability of these findings.

Conclusion—The association between some stressful life events and MDD seems to be moderated by age, underscoring the need to examine specific events, as well as clusters of events. Better understanding of such interactions may facilitate early identification of possible risk factors for pediatric MDD.

Keywords

depression; children; adolescents; childhood depression; stressful life events; age and sex interaction

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Introduction

Depression among adults has been associated with various stressful life events during their childhood years (e.g., Gilman et al., 2003; Hill et al., 2004). Studies of children and adolescents also have reported links between depression and stressful life events (e.g., Franko et al., 2004; Ge et al., 1994; Hetherington & Hagan, 1999; Silberg et al., 1999; Sund et al., 2003). To better understand this relationship, stress events have been examined in various ways, such as total number of events experienced during specified time intervals (e.g., Williamson et al., 1995), event clusters defined on conceptual, clinical, or practical grounds (e.g., Williamson et al., 2005), and specific individual events (e.g., Weller et al., 1991). However, it is not clear whether these different approaches to life events yield comparable or uniquely useful information in the context of pediatric depression.

Researchers have also examined whether the association between life events and pediatric depression is moderated by age and sex. For example, in a 4-year longitudinal study of a community-based sample, Ge et al. (1994) reported that the number of uncontrollable events and depressive symptoms were associated among girls but not boys. Bauma et al. (2008) also found that the association between stressful life events and depressive symptoms was stronger for girls than for boys. Correlations between stressful life events and depression also have been reported during various developmental periods including pre-school (Luby et al., 2006), pre-adolescence (Ge et al., 1994; Williamson et al., 2005), and adolescence (Nolen-Hoeksema et al., 1992; Williamson et al., 1995). Yet, the nature of the interaction of developmental periods (or age) and sex is still unclear. For example, Williamson et al. (2005) found that pre-adolescent, depressed girls experienced more “child independent” life events than did anxious or normal comparison girls, whereas among adolescents the reverse pattern was detected (Williamson et al., 1995). Rudolph and Hammen (1999) found that in a sample of diagnostically heterogeneous, clinically referred youths, the likelihood of child-independent stressful events remained stable from childhood to adolescence, but there was a significant increase in child-dependent events (events that may be caused by the child’s own behavior) during adolescence, especially among girls.

Surprisingly, and despite the ongoing interest in the role of stressful events in depression, there is a scarcity of research with clinical samples of diagnosed depressed youth. We identified only four studies of depressed pediatric samples that compared clinical cases with normal controls (Goodyer et al., 1988; Horesh et al., 2003; Williamson et al., 1995; 2005), and two studies that compared depressed youths and youths with other psychiatric diagnoses (Benfield et al., 1988; Berney et al., 1991). However, these studies have included small samples, which constrain both the interpretation and generalizability of the findings. For example, Williamson et al. (2005) compared 45 depressed children and 11 normal controls and reported that depressed children, and females in particular, were more likely to be exposed to stressful events than were normal controls. However, when Williamson et al. (1995) examined 35 depressed adolescents and 37 controls, they found no across-group differences in total life events during the year prior to the evaluation, although depressed adolescents had experienced significantly more “dependent” life events. Benfield et al. (1988), who compared 17 depressed children and 20 non-depressed psychiatric controls, also found no significant across-group differences in exposure to life events.

In summary, a few studies of depressed youth have examined the relation between life stressors and MDD by looking at total accumulation of events, various event clusters, and specific events, with some indications that these relations may be mediated by age and sex. However, given the small sample sizes in all previous studies of pediatric depression, neither the relative usefulness of the various ways of examining life events nor their associations with sex, age, or their interactions have been well explored. Given the availability of a very large clinical sample

of depressed children and adolescents and a similarly large sample of school-based comparison youths, the present study had two goals: a) to examine stressful life events as total cumulative events, clinically meaningful event clusters, and/or individual events and b) explore whether life events were moderated by age, sex, and their interactions.

Methods

Participants

The clinical sample consists of 434 depressed children who had been participating in a study of genetic and psychosocial risk factors for childhood-onset depression, and were recruited through 23 child psychiatric facilities across Hungary. To be included, children had to be 7.0 years to 14.99 years old, meeting DSM-IV criteria for a mood disorder, and have at least one available biological parent and one biological sibling in a similar age range (not included in the present analysis). The clinical sample included 199 females (mean age 12.1 years) and 235 males (mean age 11.1 years). The mean age of MDD onset for the sample was 10.8 years (SD = 2.2). The control sample consists of 724 children from three elementary schools (grades 1 to 8; ages 7 to 14.11) in Szeged, Hungary (population approximately 200,000). The control sample included 399 girls (mean age 10.8 years) and 325 boys (mean age 10.8 years). We excluded subjects with mental retardation or any major systemic medical disorders.

Procedures

Enrollment and assessment procedures for clinical cases have been described in detail previously (Kapornai et al., 2007; Kiss et al., 2007). In brief, psychiatric diagnoses were verified via a 2-part evaluation conducted by different clinicians at approximately 6 weeks apart. The first evaluation included a) the Mood Disorders section of a semi-structured psychiatric interview, the Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D), which is an extension of the Interview Schedule for Children and Adolescents (ISCA; Kovacs, 1985; Sherrill & Kovacs, 2000) and b) an extensive demographic data form, the Intake General Information Sheet (IGIS). Children who met DSM-IV criteria for mood disorder at the first evaluation were then assessed further using the complete ISCA-D; independent, trained psychiatric diagnosticians provided the final diagnoses.

We obtained data from the normative sample via parent-completed and child-completed questionnaires. Children in the required age range, attending elementary schools in Szeged, took home a packet of forms that included a consent form, self rating scales, and a short version of IGIS (see below) for parents. We enrolled children whose parent or legal guardian signed the consent form and completed the questionnaires. The forms were returned to the school and were collected in a locked box. Of the 2,033 parents contacted, 1,333 (65.6%) agreed to participate. The present analysis used the IGIS of children who met age criterion for our main study.

Life events were abstracted from the Intake General Information Sheet (IGIS), a fully structured data sheet covering demographics, as well as key events pertaining to the family, the subjects' development, physical health, psychosocial history, and a range of stressful life events, which was completed based on an interview with the parent. In the school-based comparison sample, parents completed on their own an abbreviated version of the IGIS.

The present article considers 26 stressful events. For each, the parent reported whether the child ever experienced the event. In addition to a total score (ranging from 0 to 26) reflecting the number of events experienced, twenty-two of the events could be grouped into 4 clinically meaningful clusters. The 4 event-clusters are: a) "*Parental health*": hospitalization, physical illness, or psychiatric illness of biological or stepparents; b) "*Death of close relatives*": parental,

or other death in the family; c) "*Sociodemographic*": financial problem, moving, parental unemployment, natural disaster, loss of home; and d) "*Intrafamilial*": birth, hospitalization, psychiatric illness of sibling, foster care, family arguments, and divorce of biological parents.

Statistical Approach

To examine the association between total events and key demographic variables, we conducted separate ANOVAs for the MDD and comparison samples, with total events as dependent variables, and sex, age, or age-by-sex interactions as independent variables. We examined associations between the four event clusters and MDD diagnosis by means of logistic regression analyses after adjusting for demographic across-group differences. Hierarchical logistic regression models were employed to examine specific events within each cluster (model 1), and their interactions with sex (model 2), age (model 3), and sex by age (model 4), as predictors of MDD diagnosis. We used Likelihood ratio tests (LRT) to compare model fit.

Results

Total Life Events

According to their parents, depressed youngsters experienced twice as many events (6.0 ± 2.8) than did the school-based cohort (2.8 ± 2.0). Age was unrelated to total number stressful events in the depressed sample ($r = 0.05$; $p = 0.29$), while a weak but statistically significant positive correlation was observed in the school-based cohort ($r = 0.15$; $p<0.01$). Figure 1 depicts the number of life events across age groups for the two samples. As shown, for the depressed sample, comparable total life events were reported across the various ages (5.5 – 6.5 events). However, within the comparison group, we noted an increasing number of stressful events as a function of age, ranging from 2.5 events at age 7 to 3.5 events at age 14.99.

Consistent with the bivariate associations reported above, results of the ANOVA indicated that age and total number of events were significantly associated in the *comparison sample*, $F(1,720) = 17.05$, $p<0.01$. We did not observe a sex effect, $F(1,720) = 0.01$, $p =0.92$, or age-by-sex interaction, $F(1,720) = 0.00$, $p = 0.99$, in this sample. In the depressed sample, the number of stressful events reported by parents did not vary by children's age, $F(1,430) = 1.12$ $p = 0.29$, or sex, $F(1,430) = 1.88$, $p = 0.17$, and there was no age-by-sex interaction, $F(1,430) = 0.08$, $p = 0.78$.

Event Clusters

Adjusting for age and sex, the odds of being in the depressed group significantly increased as a function of three out of four event clusters, namely: parental health, death of close relatives, and intra-familial events; the increases in odds were 61%, 105%, and 107% respectively (see Table 1). Parental health events as well as death of relatives also significantly interacted with age; thus, younger children who experienced these events were more likely to be in the depressed group than were older children who experienced similar events.

Specific Events

Table 2 presents the rate of endorsement and adjusted odds ratio of each specific event based on the final selected hierarchical model within each cluster. Nearly all *parental health events* were associated with an increased risk of MDD ($R^2 = 0.22$, LRT $\chi^2(8) = 150.14$, $p < 0.001$). Adding age interactions to parental health events accounted for significantly more variance ($R^2 = 0.25$, LRT $\chi^2(7) = 26.40$, $p < 0.001$). Specifically, the risk posed by physical illness of biological mother and psychiatric hospitalization of biological father decreased significantly with children's age. Adding sex or sex-by-age interactions did not significantly improve the model.

Both events in the *death of close relatives* cluster were significantly associated with MDD ($R^2 = 0.136$, LRT $\chi^2(2) = 64.37$, $p < 0.001$). Age interactions also were significant ($R^2 = 0.144$, LRT χ^2 (2) = 7.23, $p < 0.027$), suggesting that the risk of being in the MDD group posed by the death of a close relative decreased with age. Additional interactions with sex or the sex-by-age were not significant. All *sociodemographic events* were significantly associated with MDD ($R^2 = 0.14$, LRT $\chi^2(5) = 67.69$, $p < 0.001$). Significant age interactions ($R^2 = 0.15$, LRT $\chi^2(5) = 13.96$, $p = 0.016$) revealed that the association between loss of home and MDD decreased with age. Interactions with sex or the sex-by-age were not significant. *Intrafamiliar events* were associated with MDD ($R^2 = 0.29$, LRT $\chi^2(6) = 223.35$, $p < 0.001$); significant age interactions ($R^2 = 0.32$, LRT $\chi^2(5) = 29.98$, $p < 0.001$) indicated that the association between MDD and sibling birth and parental divorce decreased with age. However, interactions with sex-by-age were also significant ($R^2 = 0.34$, LRT $\chi^2(5) = 11.49$, $p = 0.043$). For girls, the risk of MDD posed by sibling psychiatric illness decreased with age, while for boys this risk was relatively constant. Finally, three of the four *miscellaneous events* were significantly associated with MDD ($R^2 = 0.46$, LRT $\chi^2(4) = 419.92$, $p < 0.001$), but showed no significant age, sex, or sex-by–age effects.

Discussion

Based on the largest clinical sample of depressed children and adolescents to date, we found that young patients with MDD experienced about twice as many lifetime negative events than did a school based comparison group. Out of 26 stressful major life events queried, children in the comparison sample experienced an average of 2.8 events during their lives, while our depressed patients reportedly experienced an average of 6.0 events. Notably, the rate of total lifetime stress events in our Hungarian, school-based comparison group is comparable to that in normative USA samples reported by studies that queried a similar number of life events (Franko et al., 2004; Ge et al., 1994).

We also found that different methods of examining stressful life events in a pediatric sample with MDD provide uniquely useful information. For example, our two groups of youths differed in the *rate* of accumulation of *total* stressful events (which was not evident looking at single events): in the school-based sample, older children had accumulated slightly more events than had younger children (regardless of sex), consistent with previous research (Franko et al., 2004; Ge et al., 1994). In our clinical sample, however, age and number of life events were not associated. Therefore, our findings suggest that children with MDD experience a more rapid accumulation of stressful life events and at an earlier age than do comparison peers. Specifically, by 7- to 8-years of age, depressed children reportedly experienced more stressful life events than did 13- to 14-year-old comparison children.

Examination of event clusters as well as specific events revealed that age effects vary depending on the type of event. For example, children's age moderated the impact of parental health and familial death events. Both of these clusters seemed to be strongly associated with major depressive disorder in younger children. However, this association weakened in adolescence, possibly due to increased exposure to parental health and family death events in the comparison group during this developmental period.

Examination of specific life events (in addition to total events or event clusters) revealed that three events were highly associated with MDD. Specifically, 26% of the MDD group had experienced abuse compared to 1.5% of the comparison cases, while 56% of the depressed cases versus 7.5% of the comparison peers had experienced teasing in school. Finally, 3.5% of the MDD group had a history of police contact compared to only 0.3% of the controls. These findings are consistent with reports documenting an association between childhood physical and sexual abuse and major depression in adulthood (Bifulco et al., 1987; Franko et al.,

2004; MacMillan et al., 2001; Veijola et al., 1998). Similarly, various studies have found that school teasing is associated with childhood anxiety and depression (e.g., Roth et al., 2002; Storch et al., 2004).

Finally, we failed to confirm sex or sex-by-age interaction effects on stressful events, which have been reported in clinically referred pediatric samples. For example, according to Williamson et al. (2005), girls with MDD (but not boys) experienced significantly more stressful events than did non-depressed girls, while Rudolph and Hammen (1999) reported that the number of stressful events was associated with depressive symptoms in girls (but not in boys) among children with miscellaneous psychiatric disorders. In our study, the sex by age interaction effect was limited to one type of life stress, namely a sibling having been diagnosed with psychiatric illness: the association between this event and MDD decreased with age among girls, while this association was not affected by age among boys. The differences between our findings and those of previous studies likely reflect differences in the research designs and sample sizes. For example, Rudolph and Hammen (1999) studied a diagnostically heterogenous group of clinically referred children and did not have a control group. While Williamson et al. (2005) studied a clinical MDD sample and had a healthy control group, the sample sizes were very small. The samples in the present study were sufficiently large to allow us to detect even small effects of sex (or age) on stressful events, should they exist. We therefore conclude that in the 7- to 14.9-year old age group, there are no sex differences among depressed and non-depressed youth in total lifetime exposure to stressful life events.

Limitations

Our clinical and school-based samples were not well matched geographically because the former group was recruited across Hungary through multiple sites, whereas the latter group was recruited from schools in one mid-size city. Because mothers provided retrospective information about life events experienced by their children, there is a possibility of faulty or biased recall. The control sample consisted of families who agreed to participate in the study in response to a written invitation. This raises the possibility of unknown self-selection bias within this sample. However, the clinical sample likewise included self-selected families willing to participate. Data ascertainment format (i.e., face-to-face interview versus mail-in questionnaire) also may have introduced some bias in the responses. A further limitation of our study is that each life event was coded as having (or not having) occurred, and thus multiple occurrences of a given event carried as much weight as a single occurrence. This approach is likely to have obscured more nuanced differences in life events across the two samples, especially in the older age group. Finally, the lack of a psychiatric control group means that our findings do not inform about the specificity of the results to depressed samples.

In summary, our results suggest that each of the 3 methods of examining stressful life events, namely total number of events, event clusters, and individual events, can distinguish clinic-based depressed and non-clinical comparison samples and thus the approach to be used should depend on the research question being investigated. Our results also confirm findings by others (e.g., Williamson et al., 2005) that children with MDD experience more stressful life events than do peers who are not depressed and underscore the cross-cultural or cross-national nature of these across-group trends. Importantly, the indications are that young depressed patients accumulate stressful life events rapidly and early (i.e., by the age of 7 to 9). In contras, not-depressed peers show a more gradual accumulation of life events through adolescence; a trend that appears to be the normative one. Findings that some events interact with age, and are more likely among depressed pre-adolescents than adolescents, highlight the potential importance of stress exposure during the first decade of life in the development of pediatric depression.

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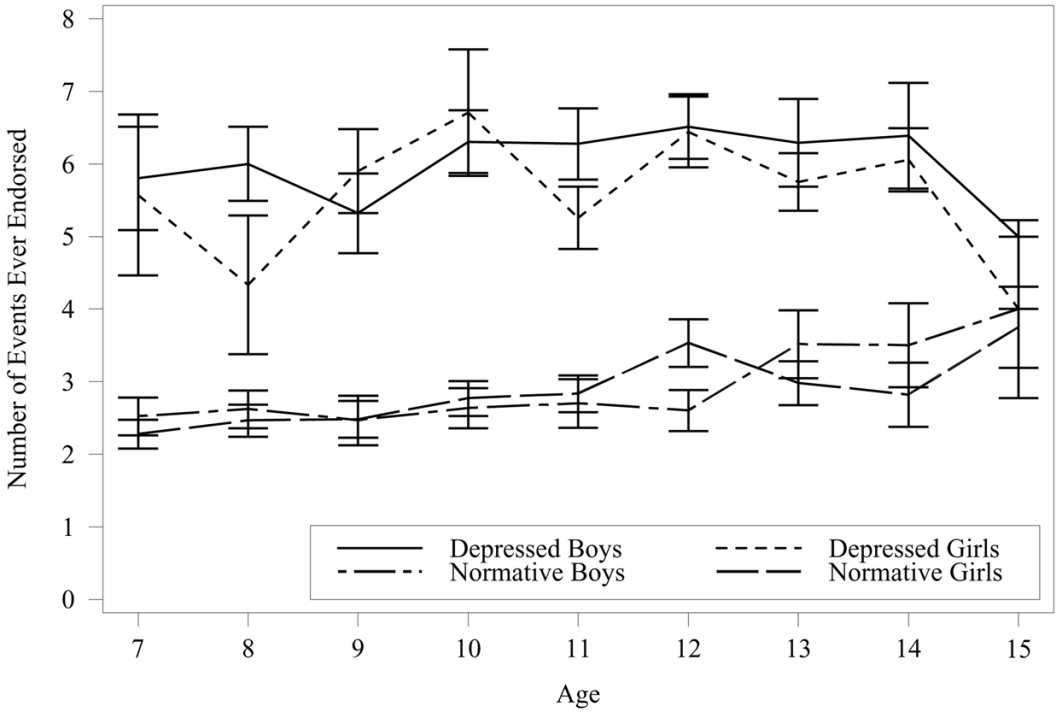

Figure 1.
Mean number of life events by age in the depressed and control sample.

Table 1

Four life event clusters as predictors of MDD: Results of Logistic regression.

	Adjusted Odds Ratio† (95% Confidence Interval)
MODEL 1 (Main Effects)	
Parental Health Event Cluster	1.61 (1.38, 1.88)***
Death of Close Relatives Event Cluster	2.05 (1.56, 2.70)***
Sociodemographic Event Cluster	1.10 (0.95, 1.28)
Intrafamilial Event Cluster	2.07 (1.78, 2.40)***
MODEL 2 (Main Effects by Age Interactions)	
Parental Health Event Cluster	1.85 (1.55, 2.20)***
-by-Age (Years)	0.86 (0.80, 0.93)***
Death of Close Relatives Event Cluster	2.27 (1.71, 3.02)***
-by-Age (Years)	0.82 (0.72, 0.93)**
Sociodemographic Event Cluster	1.10 (0.94, 1.28)
-by-Age (Years)	1.02 (0.95, 1.10)
Intrafamilial Event Cluster	2.02 (1.73, 2.36)***
-by-Age (Years)	1.01 (0.94, 1.09)

† Logistic regression results after controlling for age, sex, and age-by-sex interaction (not shown). Age measured continuously and centered at 11.

Model 1: R^2 = 0.3547, −2Log LR = 1182.85, 7 d.f. Change from Model 0: 289.49***.

Model 2: R^2 = 0.3755, −2Log LR = 1158.80, 11 d.f. Change frome Model 1, 24.05***.

* p<0.05,

** p < 0.01,

*** p <0.001.

Table 2

Reported Rates of Life Events (%) in the Patient and Comparison Samples

Event Clusters and Specific Events	Depressed Patient Sample (N= 434)	School-based Comparison Sample (N = 724)	Adjusted Odds Ratio (95% CI)
Parental Health Events			
1. Medical hospitalization of biological Mother	34.8	16.3	1.70 (1.22, 2.40)**
2. Medical. hospitalization of biological. Father	27.9	11.9	1.84 (1.23, 2.76)**
3. Medical. hospitalization of stepparent	1.6	0.3	8.15 (0.82, 81.52)
4. Physical illness of biological mother	11.3	2.3	3.54 (1.72, 7.30)***
-by-Age (Years)			0.64 (0.46, 0.89)**
5. Physical illness of biological father	7.8	2.5	1.22 (0.54, 2.78)
6. Physical illness of stepparent	0.2	0.0	n.a.
7. Psychiatric Hospitalization of biological. mother	16.4	3.8	7.04 (3.36, 14.73)***
8. Psychiatric Hospitalization of biological. father	13.2	2.7	5.36 (2.56, 11.20)***
-by-Age (Years)			0.69 (0.49, 0.97)*
9. Psychiatric Hospitalization of Stepparent	0.5	0.2	0.08 (0.00, 13.73)
Death of Close Relatives Events			
10. Death of a parent	5.3	1.4	3.47 (1.56, 7.71)**
11. Death of a close relative	71.7	48.0	2.64 (2.02, 3.45)***
-by-Age (Years)			0.85 (0.75, 0.96)**
Sociodemographic Events			
12. Financial problems	31.3	16.6	2.02 (1.48, 2.77)***
13. Move	54.4	42.9	1.33 (1.02, 1.72)*
14. Parent unemployed	46.5	29.0	1.53 (1.16, 2.01)**
15. Natural disaster	3.7	0.8	4.21 (1.46, 12.15)**
16. Loss of home	4.8	1.5	2.167 (0.93, 5.01)
-by-Age (Years)			0.67 (0.46, 0.97)*
Intra-familial Events			
17. Sibling birth	63.1	42.9	2.25 (1.52, 3.32)***
-by-Age (Years)			1.42 (1.18, 1.71)***
18. Sibling hospitalization	31.9	16.6	2.94 (1.77, 4.87)***
19. Sibling psychiatric illness	7.6	1.7	6.40 (1.62, 25.31)**
-by-Age (Years)-by-Sex (Female)			0.33 (0.13, 0.87)*
20. Family arguments	52.3	17.	2.94 (1.90, 4.56)***
21. Foster-care of subject	0.9	0.1	4.14 (0.33, 51.30)
22. Divorce of biological parents	31.8	14.0	1.64 (0.99, 2.72)
Miscellaneous Events			
23. Abuse	26.0	1.5	15.81 (7.99, 31.29)***
24. Teasing by peers	55.7	7.5	13.75 (9.58, 19.71)***
25. Police contact	3.5	0.3	11.76 (2.25, 61.45)**
26. Suspension from school	1.2	0.3	1.09 (0.10, 12.44)

Adjusted odds ratios were controlled for age and sex and other events in the same cluster.

n.a. = not available due to insufficient numbers

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

„A gyermekkori depresszió rizikótényezői" kutatás megtervezése, megvalósítása, lefolyása

13 év története: Pályázat-előkészítés, -írás és a kutatásszervezés tapasztalatai egy amerikai NIMH kutatási támogatás kapcsán

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Összefoglalás: A szerzők a közleményben összefoglalják a kutatásszervezés területén szerzett 13 évnyi tapasztalatukat. Először azokat az elővizsgálatokat ismertetik, melyek egy nagy összegű külföldi pályázat elnyeréséhez szükségesek. Azután részletezik, hogy milyen hatalmas adminisztratív apparátust igényel – a jól képzett szakemberek mellett – egy ilyen több helyen folyó kutatás felépítése, megszervezése, az adatok kezelése, azok állandó ellenőrzése és feldolgozása, értékelése. Végül ismertetik, hogy milyen tudományos eredmények vannak születőben a több mint egy évtizedes kutatómunka után.
Kulcsszavak: gyermekkori depresszió; kutatás leírása; szervezeti felépítés; közlemények

Summary: The authors summarize their experiences in research organization accumulated during 13 years. At first they outline preliminary studies which are prerequisites of high prestige international grants. Then they describe the huge administrative apparatus dedicated – besides skilled professionals – for the construction and organization of the research, the management, continuous checking and evaluation of data in such a multisite study. Finally, they report on the scientific results obtained after 13 years of hard work.
Key words: childhood onset depression; research design; organizational construction; publications

Húsz éve, hogy első alkalommal kapcsolatba léptem *Kovács Máriá*val. Olvastam a nemzetközi kutatásokban igen gyakran alkalmazott „Gyermekkori depresszió" kérdőívéről (továbbiakban GYD), és kértem, küldje el, és engedélyezze magyarra fordítását és klinikai használatát. Ő angol levelemre angolul válaszolt, de kérte, hogy a továbbiakban én nyugodtan írjak neki magyarul, mondván, hogy 1956-ban gyermekként távozott családjával hazánkból, s így olvasni és beszélni jól tud nyelvünkön, de a magyar nyelvű írás már nem erőssége.

Ekkor néhány levélváltás után megszakadt a kapcsolatunk, de ő 1994-ben Magyarországra érkezett egy nagy amerikai–magyar kutatási projekt tervével „a gyermekkori depresszió rizikótényezőinek" kutatása területén. Az 5 évesre tervezett kutatást a National Institute of Mental Health (továbbiakban NIMH) támogatásával képzelte el, de mint nagy tapasztalatokkal rendelkező kutató tudta, hogy egy ilyen volumenű projekt elnyeréséhez és külföldi lebonyolításához rendkívüli erőfeszítéseket kell tenni.

Előkutatás

Először is meg kell győzni az NIMH-t, hogy miért fontos ez a téma. Miért kell ezt Magyarországon és nem az USA-ban végezni. Magyarországon megfelelő kutatóbázis kialakítható, és a kutatásban résztvevők alkalmasak arra, hogy a kutatást lefolytassák.

Ahhoz, hogy mindezt bebizonyíthassuk, egy kisebb előkutatást kellett megtervezni és elvégezni, amihez a Fogarty International Research Collaboration Award támogatását kértük a „Depression and Suicidal Behaviors in Hungarian Children (5 R03 TW00459-02)" című pályázatban, melynek a koordinátora *Csorba János* volt.

Támogatási összeg: 14 895 dollár

A kutatás fő célja: Megvizsgálni, és adatokkal alátámasztani, hogy Magyarországon vegyes gyermekpszichiátriai klinikai betegcsoportban milyen a gyermekkori depresszió és öngyilkossági viselkedés pont prevalenciája.

Ehhez három gyermekpszichiátriai intézet együttműködése volt szükséges. A kutatásban a Semmelweis Egyetem Pszichiátriai Klinika Ifjúságpszichiátriai Szakrendelése, a Vadaskert Alapítványi Kórház Gyermekpszichiátriai Osztály és Szakambulancia és a Szegedi Tudományegyetem Gyermek- és Ifjúságpszichiátriai Önálló Osztály fekvő- és járóbeteg részlegei vettek részt.

A felmérés a következőkből állt: Olyan strukturált interjú (Detailed Evaluation Schedule for Children and Adolescents – DESCA) felvétele, mely tartalmazza az öt gyermekpszichiátriai részlegen az újonnan jelentkezett gyermekek és családjuk szocio-demográfiai paramétereit, nagyobb életeseményeit, pszichoszomatikus fejlődési adatait és pszichopatológiai tüneteit. Az interjút részben a szülővel, részben a gyermekkel arra kiképzett gyermekpszichiáterek és pszichológusok készítették. Emellett egy nemzetközi kutatásokban gyakran alkalmazott önkitöltős kérdőívet vettek fel a szülővel a gyermek általános pszichopatológiai tüneteiről Childhood Behavior Checklist (továbbiakban CBCL), és a gyermekkel kitöltették a GYD feladatlapot, mely specifikusan a depresszió tüneteire kérdez.

A kutatás négy fázisa

Instrumentáció: a DESCA magyarra fordítása, visszafordítása angolra, majd a magyar változat további finomítása egy bilingvis pszichológus segítségével. A GYD feladatlap és a CBCL hiteles magyar fordítása már rendelkezésre állt.

Interjúkészítők kiképzése: 10 gyermekpszichiáter és 2 pszichológus kiképzése a következőkből állt: DESCA itemenkénti elemzése, szerepjáték a résztvevőkkel, és 2–2 interjú a beteggel a kiképző, *Kovács Mária* jelenlétében.

Interrater reliabilitás: 68 betegnél 2 interjúkészítő volt jelen az interjú felvételénél: az egyik az interjút készítette, a másik tőle függetlenül pontozta az interjút. Az interrater reliabilitás elfogadhatónak bizonyult (Kappa≥0,85) a DESCA itemek 80%-ánál.

Fő tanulmány: 1996. október és 1997. október között a három betegfelvételi iroda szűrte a betegeket. A gyermek bekerülhetett a kutatásba, ha 7–17 év közötti volt, nem volt mentálisan retardált, nem volt krónikus gyermekgyógyászati/neurológiai betegsége, legalább egy biológiai szülővel élt együtt, aki a gyermekről megbízható információt tudott nyújtani. A szülőt és gyermeket, ha a vizsgálatba bekerülési kritériumoknak megfelelt, felvilágosítottuk a kutatás lényegéről, és beleegyezését kértük a vizsgálat lefolytatásához. A DESCA interjú felvétele és az önkitöltős kérdőívek a beteg és a szülő számára kb. 1–1,5 órás elfoglaltságot jelentett. Cserébe a beteg és a szülő egy szokásosnál részletesebb, a gyermek lelkiállapotát jobban tükröző gyermekpszichiátriai vizsgálatot kapott.

A klinikai diagnózist (depressziós vagy más pszichiátriai betegség) a strukturált interjú, a szülő és gyermek által kitöltött önkitöltős kérdőívek, valamint egy nyitott interjú alapján a vizsgálatot végző gyermekpszichiáterek véleményének figyelembevételével állapítottuk meg.

Az adatokat a projekt statisztikusához küldtük, ahol az interjúk és kérdőívek ellenőrzésen mentek át, a kihagyott válaszokat a szülővel/gyermekkel telefonon pótoltattuk.

Eredmény

90%-os beleegyezési arány mellett 490 beteg került a kutatásba, ami igen jónak mondható. Általában az anyák voltak az informátorok. A gyerekek 58%-a élt érintetlen családban, szemben

az USA-ban észlelt 26–36%-os aránnyal. A gyermekek 83,9%-ának volt legalább egy testvére.

A következő, a támogatás szempontjából fontos szempontnak (7–14 éves életkor közötti résztvevők) felelt meg 392 gyermek. A DESCA interjúra alapozva 34,4%-uk merítette ki a major depresszió DSM-IV szerinti diagnosztikus kritériumait. Ebben a fiatalabb depressziós alcsoportban a nemi megoszlás, a testvérszám és az intakt családok száma a nagyobb csoporthoz hasonló volt. A depressziós gyermekek testvérei és unokatestvérei között lényegesen gyakoribb volt a depressziós anamnesztikus adat, mint a nem depressziós betegek esetében (chi-négyzet=6,67; p=0,01 chi-négyzet 11,15, p=0,001).

Ezek alapján az NIMH-nek bebizonyíthattuk, hogy Magyarországon magas a major depresszióban szenvedő gyermekek száma, akik közül többen élnek biológiai szüleikkel együtt, mint az Egyesült Államokban, és különböző intézetek között létrehozható olyan kutatói együttműködés, mely biztosítja az adatok egyöntetű felvételét, a kidolgozott protokoll betartását.

A gyermekkori depresszió rizikótényezői (NIMH PO1-MH 56193) kutatás 1998. december 1.– 2007. június 31.

A fenti – Fogarthy-kutatás – adataiból kiindulva elkezdhettük az előbb három évre tervezett depresszió kutatás pályázatának megírását, melyet az 1998-as tavaszi benyújtás után revízióra visszaküldtek, de az ismételt beadást követően, majd a 2007-ig történő meghosszabbítás kérelmezésekor (competing renewal application) azonnal elfogadták, mely szinte példa nélkül álló ilyen nagy pályázati összegnél az NIMH történetében.

A támogatás összege 1998. december 1.–1999. november 30. között: 499.975 dollár, majd 1999. december 1.–2007. június 3. között: 2.255.797 dollár.

A kutatás célja: A gyermekkori depresszió pszichoszociális és genetikai kockázati tényezőinek vizsgálata. Megvalósítása lényegesen nagyobb szervezési feladatot (23 gyermekpszichiátriai intézet és három genetikai anyag izolálására alkalmas laboratórium együttműködését) igényelt, mint a megelőző Fogarthy-pályázat.

Etikai bizottsági vélemények kikérése: A teljes kutatási dokumentációt benyújtottuk az ETT-hez, majd engedélye birtokában valamennyi kutatóhelyen a helyi etikai bizottságokkal évente elbíráltattuk a helyben folyó kutatást.

Kutatóhelyek kiválasztása:

1. Meglátogattunk minden, egy nap alatt Budapestről vagy Szegedről elérhető gyermekpszichiátriai osztályt és ambuláns rendelést. Számba vettük a rendelő betegforgalmát, a szakorvosokat, pszichológusokat, motivációjukat a kutatásban való aktív vagy passzív részvételre. Ismertettük a kutatás céljait, és lehetőségeiket a kutatás különböző szintjein való részvételre. A kutatóhelyek feladata volt valamennyi, az ambulancián megjelenő betegnek – aki a vizsgálatba bekerülés kritériumainak megfelelt – és szülőjének elmagyarázni a kutatás lényegét, majd beleegyezésüket kérni a teljes kutatási folyamatba (két alkalommal részletes ISCA-D interjú, s amennyiben ezen depressziósnak bizonyul, vérvétel DNS-minta vételére). A bekerülési kritériumok a következők voltak: 7–14 év közötti életkor, mentálisan nem retardált, nem szenvedett krónikus belgyógyászati betegségben, legalább egy biológiai szülőjével együtt élt, volt 7–16 év közötti vér szerinti testvére, és a szülő és gyermek által kitöltött rövid depresszió szűrőteszten depresszióra gyanúsnak bizonyult.

A szűrési folyamatra a vállalkozó kutatóhely adminisztrátorait kiképeztük, majd évente emlékeztető tréninget tartottunk számukra.

Ugyancsak kiképeztük a kutatóhelyen dolgozó kezelőorvosokat a beleegyeztetési folyamatra.

2. Három genetikai laboratórium került be a kutatásba, melyek feladata a családtagoktól levett vérből a DNS izolálása, majd Torontóba – a Clarck Intézetbe – küldése volt. Torontóból *Cathy Barr* és *Jim Kennedy* meglátogatta a kiválasztott laboratóriumokat, és a DNS kivonáshoz egységes protokollt állítottak össze.

3. Mivel az NIMH szokatlanul hosszú időn át igen nagy összeggel támogatta USA-n kívüli országban a pályázatot, 3 vezető adminisztrátor

jött el Magyarországra, és személyesen meglátogatott 5 kutatóhelyet, 1 genetikai laboratóriumot, hogy képet kapjon a nagy volumenű tervek megvalósíthatóságáról.

Interjúk és kérdőívek kiválogatása, interjúkészítők kiképzése, szinten tartása, ellenőrzése

Az első lépésben 2 fő Pittsburgh-be utazott, és ott 2 hetes kiképzést kapott a féligstrukturált interjú (Kiddi-SAD) készítéséből. Ezután *Kovács Mária* és *Hartwin Sadowsky* jött Magyarországra, és angol nyelvű képzést tartott 14 főnek (közülük kerültek ki később a további interjúképzők, interjú szupervizorok, értékelő szakorvosok). Ezt követően lefordítottuk, majd bilingvis pszichológus segítségével angol nyelvre visszafordítottuk az Interview Schedule for Children and Adolescents: Diagnostic változatot (ISCA-D) és a többi kérdőívet. A korábbi Fogarthy Studyban használt DESCA interjút a kutatás jelenlegi céljának megfelelően átalakítottuk General Information Sheet (GIS) néven. Az ISCA-D felvétele – mely a pervazív zavarok kivételével valamennyi pszichiátriai betegségre rákérdez – kb. 2–2,5 órát vesz igénybe a gyermek életkorától és tünetei számától függően. Mind a szülő, mind a gyermek interjúja alapján az interjúkészítő dönt abban, hogy a kérdezett gyermeknél a tünet küszöb feletti, küszöb alatti mértékben van jelen, vagy egyáltalán nem áll fenn. (Az alkalmazott interjúk és kérdőívek felsorolását lásd az 1. táblázatban). Ezt követően azon gyermekpszichiáterek és klinikai szakpszichológusok számára, akik azt vállalták, 2 hetes interjúkészítő tanfolyamot tartottunk meghatározott tematika szerint, majd 5–5 db interjút kellett munkahelyükön elkészíteni és a szupervizorokkal megbeszélni. A továbbiakban, amennyiben a szupervizorok az 5 interjú alapján az interjúk minőségét megfelelőnek tartották, az interjúkészítők kevésbé szoros kontroll (rekalibrációs képzések) mellett elkezdhették az interjúzást.

A kutatás folyamán a kieső interjúkészítők miatt (GYED, külföldre távozás stb.) még három alkalommal tartottunk kurzus-szerű képzést, és egy egyéni, illetve kiscsoportos képzési protokollt is kidolgoztunk. Az eltelt 9 év alatt összesen 58 interjúkészítőt képeztünk ki.

A kutatásban dolgozó interjúkészítők félévente rekalibrációs továbbképzésen vettek részt, hogy a pontozásuk egységes maradjon minden kutatóhelyen.

Minden interjúról hangfelvétel készült, és az interjú szupervizorok évente randomizált módon minden interjúkészítőtől 5 hangfelvételt ellenőriztek. Ha az interjú minősége nem volt megfelelő, az interjúkészítő egyéni továbbképzésen vett részt.

Adatbeviteli rendszer kiépítése

A felvett interjúkat az interjúkészítők – a regionális irodák közvetítésével – eljuttatták a központi irodába, ahol az adatokat rögzítették egy előre elkészített adatbázisba a megfelelő adatbeviteli felület alkalmazásával. Az adatok pontosságának biztosítása érdekében a beviteli rendszer úgy működött, hogy az első bevitel után a teljes adatmennyiséget újra bevitte egy második adatbevivő (Double-check). A két bevitel során jelentkező különbségeket a rendszer végleges tárolás előtt listázta, amin végighaladva a második bevivő ellenőrizhette az eltéréseket, és meggyőződhetett a bevitt adatok pontosságáról.

A már bevitt adatokat a kutatás alatt folyamatosan ellenőriztük, egymást kizáró adat-párok, és szúrópróbaszerű ismételt adatbevitellel. Az így kapott eredmények ismeretében biztosak lehetünk benne, hogy az adatbázisban tárolt adatok kevesebb mint 0,5% adatbeviteli hibát tartalmaznak.

Pilot fázis

Mikor az összes interjú fordítása és az adatbeviteli rendszer összeállt, az első 5 bekerült eseten kiértékeltük a szűrés, az interjúkészítés, adatbevitel, vérvétel folyamatát, és a tapasztalatok alapján, ahol szükséges volt, megváltoztattuk a menetet.

1. táblázat
Az adatgyűjtés folyamata

AZ ADAT TÍPUSA	A VIZSGÁLAT IDEJE				A VÁLASZADÓ			PONTOZÁS	
	Szűrés	Bevétel		FU	Szülő	Proband	Testvér	Önkitöltős	Klinikus
		I.	II.						
Pszichiátriai tünetek									
Előszűrés	+				+	+		+	
Klinikai szűrő	+			+	+	+			+
ISCA-D hangulat modul		+			+	+	+		+
ISCA-D			+		+	+	+		+
FIGS-M		+			+				+
CASFI-M		+			+				+
Gyerek tünetlista (CSC)		+		+	+			+	
CBCL		+		+	+			+	
BDI			+		+			+	
CDI		+		+		+	+	+	
Gyerek Reménytelenség Skála		+		+		+	+	+	
Spielberger Vonás/állapot Szorongás Skála			+		+			+	
Demográfiai és életesemények									
Bekerülési Általános Információk Kérdőív (GIS)		+			+				
Utánkövetéses GIS (FU-GIS)				+	+				
Életminőség (QL)		+		+	+	+	+	+	
Érzelmi reguláció									
EAS Temperamentum Kérdőív		+		+	+			+	
Érzések és a Gyermekem			+		+			+	
Felnőtt Attachment Skála (AAS)			+					+	
PANAS-X		+		+		+	+	+	
PANAS-M		+		+		+	+	+	
Érzelmi válasz depresszióra (RDQ-Y)		+		+		+	+	+	
Élet Orientáció (LOT-Y)		+		+		+	+	+	
Érzések és Én		+		+		+	+	+	
Milyen vagyok (Harter's önértékelési profil gyermek vagy serdülő változat)									

FU=follow-up; **ISCA-D**=Interview Schedule for Children and Adolescent-Diagnostic Version; **FIGS-M**=Family Interview for Genetic Screening-Modified Version; **CASFI-M**=Child-Adolescent Screen for Family Interview-Modified Version; **CSC**=Child Symptom Check List; **CBCL**=Child Behavior Check List; **BDI**=Beck Depression Inventory; **CDI**=Children's Depression Inventory; **GIS**=General Information Sheet; **AAS**=Adult Attachment Scale; **PANAS**=Positive and Negative Affect Schedule **RDQ-Y**=Responses to Depression Questionnaire for Youngsters; **LOT-Y**=Life Orientation Test for Youngsters

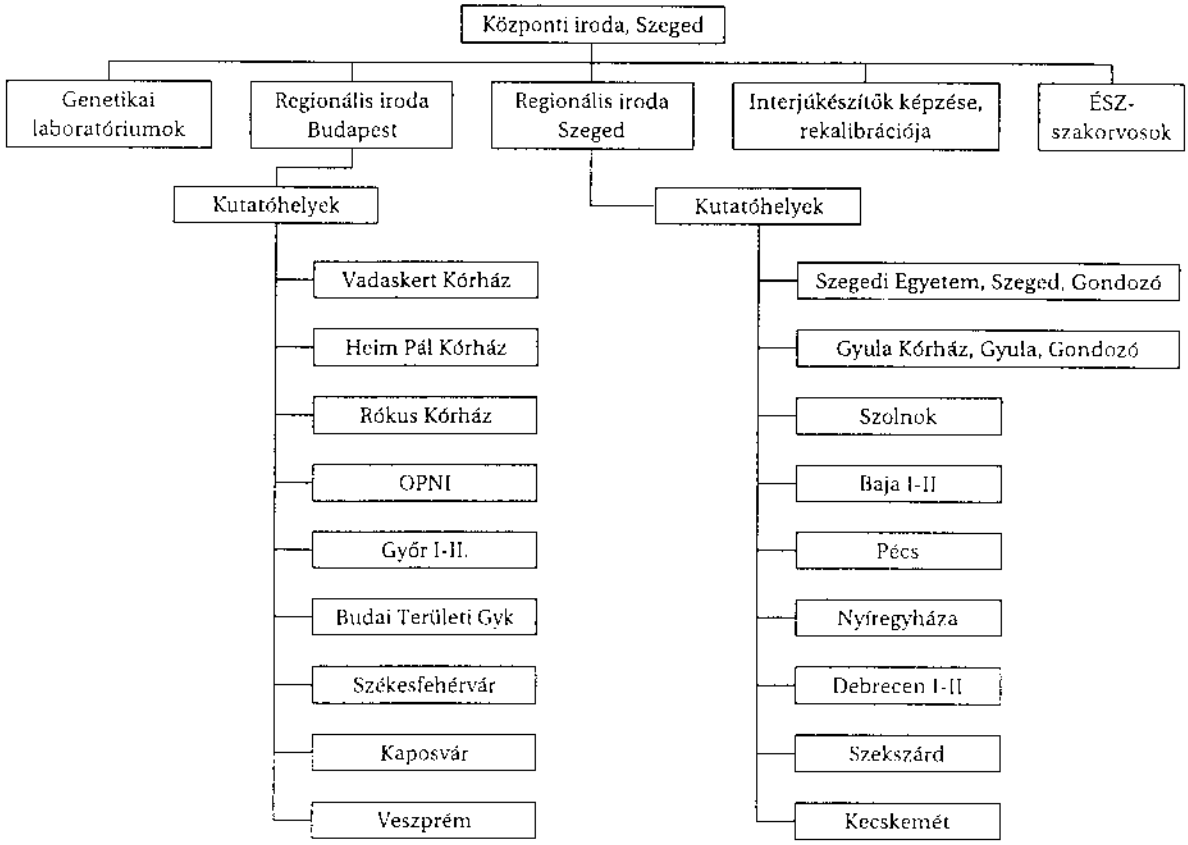
Adminisztratív infrastruktúra megszervezése

Ezt követően, hogy a szűrés, interjúkészítés, vérvétel stb. mindenütt egységesen történjen, minden folyamatot írásos protokollban rögzítettünk. A protokollok írása, a protokoll szerinti működések monitorizálása, a kutatás összefogása egy központi iroda felállítását tette szükségessé. A kutatás szervezeti felépítése az alábbi volt. (1. ábra)

Kutatóhelyi adminisztrátor feladatai

A 23 kutatóhelyen valamennyi megjelent betegen ellenőrizni, hogy megfelel-e a bekerülési

1. ábra
A kutatás szervezeti diagramja



kritériumoknak, és ezt az adott táblázatba a betegek kezdőbetűit alkalmazva feljegyezni. A táblázatot naponta telefaxon elküldeni a regionális központba. Ha a beteg a bekerülési kritériumoknak megfelelt, akkor odaadni neki a beleegyező nyilatkozatot, majd tájékoztatásra és beleegyezésre a kezelőorvoshoz küldeni. Ha a szülők és a gyerek a kutatásban való részvételbe beleegyeztek, jelenteni a regionális központba, és elküldeni a beleegyező nyilatkozatot. Ezután biztosítani, hogy a központ által szervezett interjúkészítőnek a megszervezett időpontban legyen a kutatóhelyen helye az interjú elkészítéséhez, és vigyázni a gyermekre, amíg a szülő interjúja folyik. A szűrésen átesett gyermekeket regisztrálni a kezelőlapon, és a negatívakat félévente ismét szűrni depresszió szempontjából. Évente két alkalommal rendelkezésére kell állnia a központból kiküldött monitor számára, aki ellenőrzi, hogy a szűrési protokollt megfelelően betartják-e. A regionális központ és a kutatóhelyek közötti kapcsolat folyamatosságának biztosítására minden kutatóhelyre önálló telefont és telefaxot telepítettünk.

Regionális központok

Két regionális központot alakítottunk ki, egyet a Szegedi Tudományegyetemen, egyet Budapesten a Vadaskert Alapítványi Kórházban. A regionális központok feladata volt, hogy a hozzájuk tartozó kutatóhelyekkel napi kapcsolatban legyenek, a szűrések adatait számítógépen rögzítsék. Itt szervezték meg a területükön dolgozó interjúkészítők és a kutatásba beleegyezett családok találkozásait az interjúk lebonyolítása céljából, valamint itt történt az elkészült interjúk formai és szakmai ellenőrzése, majd az interjúk elküldése a központi irodába. Minden munkafolyamatot számítógépen rögzítettek. A feladatok elvégzésére egy-egy regionális alközpontve-

zetőt, egy-egy adminisztrátort, és egy-egy interjú szupervizort alkalmaztunk.

Mindkét regionális iroda rendszeresen tartotta a kapcsolatot a hozzájuk tartozó interjúkészítőkkel. Vigyáztak, hogy ugyanahhoz a családhoz a második interjúra másik interjúkészítő legyen beosztva.

Központi iroda: Szegedi Tudományegyetem

Itt történt a kutatás valamennyi fázisának adminisztratív összefogása, az ellenőrzött interjúk adatainak számítógépre vitele, a munka elosztása.

Működtetésére manager team állt össze a kutatás általános vezetője, a kutatási koordinátor, az interjúképzési és ellenőrzési koordinátor, a gazdasági koordinátor, és az információs technológiai manager részvételével. Ez a csoport kéthetente ülésezett, megbeszélte az elvégzett feladatokat vagy a felmerült nehézségeket, és megszabta a következő 2 hétben elvégzendőket, és azok fontossági sorrendjét.

A központi iroda végezte a diagnosztikus munka utolsó fázisát is: az *Értékelő Szakorvosi folyamatok* (továbbiakban *ÉSZ*) *szervezését:* A kutatás folyamán minden betegről két interjú készült 2 hét–6 hónapon belüli időszakban 2 független interjúkészítővel. Az első alkalommal az ISCA-D-nek csak az affektív zavarok modulját vettük fel, és csak ha a gyermek ott depressziósnak bizonyult, akkor került sor a második – ekkor már a DSM-IV csaknem valamennyi betegségét felölelő teljes ISCA-D – interjúra. Az adatbevitel után az interjúkat kinyomtattuk és 2 értékelő szakorvos (gyakorlott gyermekpszichiáterek) a beszerzett egyéb betegdokumentációval együtt megkapta azokat. Mindketten önálló diagnózist hoztak a DSM-IV alapján, majd konszenzus konferencián döntöttek a beteg végleges diagnózisaiban, valamint abban, hogy valóban volt-e major depresszió vagy bipoláris betegsége. Ha a döntés pozitív volt, a gyermek proband státuszt kapott.

Ezután kerülhetett sor a *biológiai mintavételre*, melyet szintén a központi iroda szervezett. Minden betegtől, és lehetőleg mindkét szülőjétől szájnyálkahártya kenetet és vért is vettek, s a központban generált kódszámmal látták el azokat, így biztosítva azok teljes anonimitását. Ha egy testvér depressziósnak bizonyult, tőle is vettünk biológiai mintát. A szájnyálkahártya mintát azonnal Torontóba küldték, míg a vért valamelyik hazai genetikai laboratóriumba DNS izolálásra, elkerülendő a feldolgozás során a családon belüli vizsgálati anyagok esetleges összecserélését.

A kutatás utolsó fázisa az *utánkövetéses vizsgálat* volt, szintén a központi iroda szervezésében. Minden major depressziós betegnek és 7–16 éves testvérének évente kiküldtünk egy önkitöltős tesztcsomagot, amelyben a szülő és a gyermekek által kitöltendő, a depressziót és a bipoláris betegséget szűrő tesztek voltak. Célja az volt, hogy megtudjuk van-e visszatérő depressziós epizódja a probandnak, vagy nem csapott-e át bipoláris betegségbe. Emellett, ha a testvérnél a depresszió gyanúja merült fel, akkor őt is a probandnál leírt diagnosztikus folyamatnak vetettük alá, s ha major depresszió betegség vagy bipolaritás igazolódott, tőle is DNS-mintát vettünk.

A kutatás menete és eredményei

Szűrés, bevonás, beleegyezés: A lehetséges probandok szűrését 1999. november 1. és 2005. július 1. között végeztük. Összesen 28 533 gyermeket szűrtünk, akik közül 1299 adott a szűrőkérdésekre a határértéknél magasabb pontszámot, és 840-en egyeztek bele a kutatásban való részvételbe. További 403 eset került be a kutatásba alternatív úton. Ezekről a betegekről a kezelőorvosok gondolták, hogy depressziósak és irányították a kutatáshoz őket. Ebből a 403 esetből 256-an egyeztek bele a részvételbe.

Diagnosztikus folyamat: Összesen 1023 pozitív szűrési eredménnyel rendelkező gyermeknek 1127, míg 406 testvérnek 474 első interjúja volt az interjúzási fázis végéig. A fenti csoportból 762 probandnak 768, míg 222 testvérnek 233 második interjúja volt. 756 probandot és 200 testvér adatait értékelték az Értékelő Szakorvosok (1127 és 267 ÉSZ értékelés). Az értékelések eredmé-

nyeként 723 probandnál és 182 testvérnél igazolódott a depresszió. (Az eltérő számok egyrészt abból adódnak, hogy voltak olyan betegek, akiket az eltelt évek során 2–3 alkalommal is interjúvoltunk, mivel első, illetve második alkalommal nem merítették ki a major depresszió DSM-IV diagnosztikus kritériumait. Másrészt abból, hogy relapszus, rekurrencia, esetleg bipolaritás gyanúja esetén a proband ismét interjúra került). Kontrollcsoportként 104 olyan 18 éven felüli testvért is bevontunk a kutatásba, akiknél a fentebb említett részletes diagnosztikai folyamat egész életükre vonatkozóan kizárta major depressziós epizód fennállását.

Interjúban adott diagnózisok ellenőrzése: A kutatásban résztvevő interjúkészítők által felvett interjúk minőségét rendszeres rekalibrációs találkozókkal biztosítottuk. Évente két alkalommal országos találkozót szerveztünk az interjúkészítőknek. Ezeken a találkozókon az Értékelő Szakorvosok is esetmegbeszéléseket tartottak a magyarországi vezető kutató irányításával, így biztosítva az ÉSZ értékelések egyöntetűségét.

Minden elkészült interjút egy héten belül formailag és tartalmilag ellenőriztünk. Telefonon nem megoldható probléma, hiba esetén az interjút visszaküldtük javításra a készítőjének. A szupervízorok rendszeresen ellenőrizték az interjúkat a magnókazetták visszahallgatásával.

Elvesztett alanyok: 74 gyermeket/családot elveszrettünk még az első interjú előtt, 210 eset vált a kutatás számára nem megfelelővé, mivel nem volt érzelmi problémájuk, vagy teljesült náluk valamilyen kizárási kritérium. 130 probanddal vesztettük el a kapcsolatot, 83 esetet kizártunk, míg 23 esetben megszakítottuk a folyamatot, mivel nem kooperáltak a beleegyezést követően, és 1 gyermek meghalt a kutatás ideje alatt. 15 családdal vesztettük el a kapcsolatot költözésük miatt. 7 család esetén minden kapcsolatunk megszakadt. Ezeket az eseteket minden harmadik hónapban megpróbáltuk ismét elérni a háziorvosokon, illetve az előzetesen megadott kapcsolattartó személyen keresztül.

Vér-, nyálminta gyűjtés: Azokon a kutatóhelyeken, ahol nem volt elérhető helyi vérvevő, mobil vérvevőt alkalmaztunk, aki a vérvételt a család lakásán végezte el.

A kutatás kezdetétől vér- vagy nyálmintát 686 probandtól és 180, 18 éven aluli depressziós és 104, 18 éven felüli egészséges testvértől vettünk le. A minták családonkénti összetétele a következő: proband és két szülő (nincs érintett testvér) 339 család; proband, egy vagy több érintett testvér és 1 vagy két szülő: 251 család; proband és egy szülő: 96 család. Az összesített depressziós testvérek aránya 22,06%, ami magasabb, mint a kutatás kezdetén várt 20%.

A vér- és nyálmintákból DNS izolálás történt a helyi kutatólaboratóriumokban. Az anyag felét Torontóba küldtük további vizsgálatokra, fele pedig a hazai kutatás számára maradt meg.

Utánkövetés: Azok a gyermekek, akik az első vizsgálat során nem elégítették ki a probanddá válás kritériumait (kockázati csoport), a depressziós probandok és testvéreik mindannyian évente levélben küldött önkitöltős tesztet kaptak. A kutatás kezdetétől 904 proband+ kockázati csoportban lévő gyerek, valamint 1151 testvér kapott önkitöltős kérdőívet, az évek során összesen 5044 levelet küldtünk ki. 888 proband + kockázati csoportban lévő gyermek és 1112 testvér mindösszesen 4688 alkalommal küldte vissza a kérdőívet. Az összesített visszaküldési arány 92,9% volt. A válaszok értékelése után összesen 382 utánkövetési interjút készítettünk probandokkal és 65-öt testvérekkel.

Kapcsolattartási célból 2008. augusztus 1–31. között 1077 utánkövetéses önkitöltős kérdőívet küldtünk ki, 2008. december 31-ig a kérdőívek 78%-a érkezett vissza.

Adat-integritási folyamat: A kutatás ideje alatt 2 teljes állású és 1 félállású adatbevivő dolgozott a kutatásban. Egy monitorizáló csapat biztosította az adatok integritását, valamint a különböző folyamatokban észlelhető hibáknak a felderítését. Az adatellenőrzési csapatot 1 teljes állású és 3 félállású adminisztrátor alkotta.

Felmerülő problémák, megoldások, megelőzések

Három hónapos célokat állítottunk fel a levélben küldött utánkövetési folyamat optimalizálására és az adattisztításra. Az eredményeket minden

három hónap végén, országos megbeszéléseken átnéztük, értékeltük ez előző 3 hónap eseményeit és újabb feladatokat tűztünk ki a következő 3 hónapra.

Megpróbáltuk minimalizálni az elvesztett családok/gyermekek számát, ezért több lépcsős eljárást dolgoztunk ki az elvesztett családok követésére. Ennek keretében próbáltuk elérni a családot telefonon, telefonszám és címkeresési eljárásokat, ajánlott levelek küldését alkalmaztuk, valamint a Népességnyilvántartóból próbáltuk megtudni az elvesztett családok elérhetőségét. Minden elvesztett családot 3 havonta próbáltunk a fenti módszerekkel a kutatásba visszahozni. Erre a folyamatra külön csoportot szerveztünk.

Főbb eredmények

Együttműködés: A sok éves együttműködés és együttgondolkodás a csaknem egész Magyarországot felölelő gyermekpszichiátriai ellátásban és gondozásban részt vevő kollegákkal javította és egységesítette diagnosztikai munkánkat a mindennapi betegellátásban, és szellemi erőforrást jelentett mindenkinek, de főleg az izoláltan, nehéz körülmények között dolgozó, de fejlődni kívánó munkatársainknak.

Standardizált tréning: Magyar nyelvre adaptáltunk egy korábban hazánkban nem alkalmazott féligstrukturált pszichiátriai diagnosztikus interjút (ISCA-D), mely a legtöbb pszichiátriai betegség DSM-IV szerinti lehető legpontosabb diagnózisát adja. Kidolgoztunk egy standardizált tréningprogramot a féligstrukturált diagnosztikus interjúkészítéshez. Ennek felépítése: 2 hetes bevezető tréning (elméleti és gyakorlati jártassággal rendelkezőknek a pszichiátriai diagnosztikában és a féligstrukturált interjútechnikában) majd 3 napos gyakorlatokat szerveztünk 3 havonként.

Infrastruktúra, informatika: Megterveztünk és kiviteleztünk egy komplex informatikai megoldást az ország 3 kutatási irodájában, felállítottunk egy egyedülálló adatbázist, és egy webes felületet az adatok tárolására, kezelésére, valamint az interjúk szervezéséhez. Az adatok integritását kettős adatbevitellel és folyamatos adattisztítással biztosítottuk. Komplex tűzfal rendszer és Virtuális Magánhálózatok (VPN) biztosították a kódolt, biztonságos kommunikációt az irodák között. Napi mentés készült az adatbázisról, és a mentéseket a szerver háttértárolóján, egy különálló backup tároló szerveren, valamint heti rendszerességgel CD-re/DVD-re mentve tároljuk.

Adatbázis és biobank: A kutatás folyamán olyan adatbázist állítottunk össze a gyermekkori kezdetű depresszió területén, mely világviszonylatban is egyedülálló, mind a kivizsgálás és *diagnosztika precizitása*, mind a *probandszám nagysága* miatt. Biobankunkban a DNS-minták mellett számos pszichoszociális kockázati tényező vizsgálatára is van mód, mely lehetővé teszi a genetikai eltérések összekapcsolását a betegség kialakulásában résztvevő egyéb faktorokkal.

Publikálás

2003 decemberétől kezdve rendszeres, havi kutatási találkozókat tartottunk. A megbeszélések célja volt, hogy elősegítsék és felügyeljék a publikációs munkákat. A szupervíziót a kutatás magyarországi vezetője – *Vetró Ágnes* – és a helyettese – *Gádoros Júlia* – tartották.

Számos tudományos cikket publikáltunk, vagy van jelenleg bírálat alatt, és számos előadást tartottunk országos és nemzetközi konferenciákon, jóllehet az adatoknak még csak egy kis töredékét sikerült elemeznünk. Két kollegánk PhD fokozat eléréséhez szükséges abszolutóriumot szerzett, s téziseinek megvédése előtt áll. Három kollegánk elkezdte PhD témája kidolgozását.

Genetika

Számos, főként a szerotonin anyagcserében szerepet játszó gént vizsgáltunk (Lásd tudományos közlemények). Vizsgálataink szerint a gyermekkori kezdetű depresszió kialakulásában az ESR1, NTRK3, MTHFR, AVPR1B géneknek és a BDNF-nak lehet szerepe.

Pszichoszociális kockázati tényezők

A nehéz temperamentum a major depresszió és az első internalizációs kórkép korábbi jelentkezésére hajlamosít, de csökken ez a hatás, ha a gyermek teljes családban él a korai gyermekkorban. A nehéz temperamentumnak ez a hatása az életkor előrehaladásával csökken.

Magas diszfunkcionalitás és alacsonyan funkcionáló érzelmi regulációs tendencia növeli az öngyilkossági hajlam esélyét depressziós gyermekeknél, míg a negatív jellegű emocionalitásnak nincs semmi hatása.

Összehasonlítva az anyától és a gyermektől kapott válaszokat a gyermek depressziós tüneteiről, azt találtuk, hogy a lányok sokkal súlyosabb tünetekről számolnak be mint a fiúk, ugyanakkor az anyák válaszában nincs nemenkénti eltérés. A szülő–gyermek egyezés a tünetekben függött a gyermek életkorától. A depressziós anyák sokkal súlyosabb problémákról számoltak be gyermekükkel kapcsolatban, mint a nem depressziósak.

Major depresszió és a komorbid szorongási zavar növeli az alkoholfogyasztás esélyét. A legmagasabb kockázat a generalizált szorongáshoz köthető (OR=8,4). Komorbid viselkedési zavarok növelik a dohányzás kockázatát (OR=3,72).

A projekt ideje alatt a kutatáshoz a betegektől vagy a kutatóhelyektől panasz, vagy etikai kifogás nem érkezett.

Összefoglalva elmondhatjuk, hogy amikor elkezdtük írni a pályázatot még magunk sem gondoltuk, hogy ilyen szerteágazó, komplex, nagy volumenű lesz a kutatás, melyet lefolytatunk. A pályázat megvalósításán 14 teljes munkaidőben dolgozó munkatárs dolgozott, de az eseti interjúkészítőkkel, részmunkaidős kollegákkal együtt voltak olyan hónapok, mikor 114 embernek számfejtettünk bért. Mindez természetesen az NIMH hatalmas támogatása nélkül nem valósulhatott volna meg, amelyért köszönetünket fejezzük ki.

Köszönetnyilvánítás

Megköszönjük a kutatásban résztvevő intézetek dolgozóinak munkáját, mely hozzásegített bennünket a gyermekkori depresszió kockázati tényezőinek jobb megismeréséhez.

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Characteristics of and Risk Factors for Childhood-onset Depression in Clinically Referred Hungarian Children and Adolescents

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Abstract

This article reports on the genetic and psychosocial risk study of childhood-onset depression (COMD) in a very large clinically referred sample in Hungary. The sample included 723 children with major depressive disorder (mean age 11.26 years, standard deviation [SD] 2.09, range seven to 14.9 years) recruited from 23 clinical sites across the country. Psychiatric evaluations were conducted via a semi-structured interview and diagnoses were assigned by *Diagnostic and Statistical Manual of Mental Disorders-IV* (DDSM-IV) criteria. Developmental and life events were queried via a structured questionnaire. Children and parents also completed self-rated questionnaires that assessed various symptoms, aspects of temperament, emotion regulation and quality of life. We report on clinical and depressive symptom presentation as a function of age, suicidality and types of sleep disturbance. We summarise findings on the relations of: emotion regulation and temperament to suicidal behaviours; early developmental characteristics and the onset-timing and severity of COMD; life events and COMD status; psychiatric co-morbidity and health risk behaviours such as smoking and drinking; mother–child agreement about depressive symptoms and quality of life of depressed children; and putative genetic contributors to COMD. Systematic and reliable empirical data and information on the defining characteristics of and risk factors associated with COMD can inform the design of preventative interventions and can also be useful to clinicians who treat children with these conditions.

Keywords

Childhood-onset depression (COMD), risk factors, symptom, severity

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This study was designed to investigate genetic and psychosocial risk factors in a large clinically referred sample of children who had their first depressive episode before 15 years of age. Cases were recruited between 1 December 1998 and 31 June 2007. Patients were screened at 23 child psychiatry centres in Hungary, the catchment areas of which covered about 80% of all referred patients in the nation. Altogether, 28,533 children presenting with various psychiatric problems were screened and 1,702 passed further screens (using pre-determined cut-off on self- and proxy-reported mood questionnaires). Consent was obtained from 1,096, of whom 905 had major depressive disorder (MDD) according to *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) criteria. We obtained samples for genetic analyses from 866 children and their parents.[1] Yearly follow-ups (across five years) were conducted via mailed questionnaires to monitor new episodes or onset of MDD. Across all years, a total of 92.9% of the monitored cases returned the questionnaires based on which subjects with probable new/recurrent episodes entered the evaluation and diagnostic process.

In this article we summarise published findings to date. Subjects in the various articles are subsamples of the total study sample; the varying sample sizes reflect the data that were available. For details, please see each of the original articles, referenced at the end of the article.

Method

Children were considered to be potential subjects if they met the following eligibility criteria: between seven and 14.9 years of age, presence of DSM-IV MDD, one available biological parent, sibling between seven and 16.9 years of age, not mentally retarded and free from major systemic medical disorders. We obtained signed informed consent from the parent and assent from the child before initial evaluation. The total sample included 723 children. Mean age at initial examination was 11.26 years (standard deviation [SD] 2.09) and 45.8% were girls. Mean age at the onset of depression was 10.11 years (SD 2.33). The average number of MDD episodes was 1.33 (SD 0.61, range one to six). Altogether, 19.5% had mild depression, 46.9% had moderate depression and 33.6% had severe depression. Twenty-eight per cent had a history of inpatient psychiatric hospitalisation and 61% had been prescribed psychotropic medication. The age of the biological mothers was 36.7 years on average (SD 6.0), they had a mean of 11.4 years of education (SD 4.3) and 37.8% came from broken families. Parent-reported financial situation was average in 59.3% of cases, below average in 31.5% of cases and above average in 9.1% of cases.

Measurements

Subjects were evaluated by a semi-structured psychiatric interview, the Interview Schedule for Children and Adolescents – Diagnostic

Version (ISCA-D).[2] It includes most DSM-IV axis I diagnoses and some DSM-III disorders. The clinician first interviews the parent about the child's symptoms and then the child, then generates an overall rating for each symptom based on the information provided by each informant. Final diagnoses were reached by consensus diagnostic procedure by best-estimate diagnosticians.[3] Psychiatric evaluations were conducted by trained child psychiatrists and psychologists. The Intake General Information Sheet (IGIS), completed based on an interview with the parent, is a comprehensive data form covering demographic, family, developmental issues, physical health, psychosocial history and life events. Parents and children also completed a variety of questionnaires. In this article, we report findings based on the following instruments: parent-rated Emotionality Activity Sociability (EAS) Temperament Questionnaire,[4] which measures four temperament dimensions: emotionality, activity, sociability and shyness; self-rated Feelings and Me child questionnaire,[5] which served as an index of children's self-regulatory responses to dysphoria and distress; child- and parent-rated Invertars zur Erfassung der Lebensqualität bei Kindern und Jugendlichen (ILK), which inquires about quality of life in seven domains;[6] and parent-rated Beck Depression Inventory (BDI),[7] which measured maternal depressive symptoms.

Results

One of the enduring questions about childhood depression is whether symptoms differ as a function of age and sex. We addressed this topic[8] given that few studies had sufficiently large samples to examine developmental differences in rates of specific symptoms. Since many depressed youths also have anxiety disorders[9] and there is an association between somatic symptoms and anxiety in childhood,[10] we also looked at the relationship between somatic complaints and depression.

Consistent with previous studies,[11,12] we found that the frequency of several neuro-vegetative symptoms, including hypersomnia, psychomotor retardation and fatigue, increased with age. This pattern was accompanied by a significant increase in depressed mood, thoughts of death and suicidal ideation and a reduction in rates of psychomotor agitation. Specifically, our results indicate that the presentation of depression becomes more neuro-vegetative as children transition from childhood into adolescence. Our findings are not entirely consistent with DSM-IV criteria, according to which irritability can substitute for depressed mood as a required symptom[13] in childhood. Depressed mood and irritability were relatively frequent across all ages, with more than 60% of patients displaying them. In contrast, anhedonia was relatively infrequent across all age groups, with rates below 50%. This suggests that anhedonia, and not depressed mood, is the least frequent core symptom in depression among children and adolescents, while irritability is significantly more common, often occurring in conjunction with rather than as a substitute for depressed mood.

Approximately 90% of depressed adults[14] and at least two-thirds of depressed children have sleep complaints,[15–17] but it is not clear whether sleep-disturbed children differ from sleep-undisturbed peers in terms of clinical presentation of the illness and whether these features differ across depressed children with insomnia, hypersomnia or both. In addressing this issue[18] we found that 72.6% of our sample had experienced sleep problems during the past month: 53.5% had insomnia, 9.0% had hypersomnia and 10.1% had both, the prevalence being significantly higher in girls. Youths with both sleep disorders were more likely to have recurrent depressive episodes, longer illness duration and highest depression severity compared with children with one disturbance only. Sleep-disturbed children had more co-morbid anxiety disorder and less oppositional defiant disorder. Depressed children with both sleep disorders may represent a severe subtype of depression with circadian rhythm disorders or sleep–wake cycle abnormalities, which may cause or worsen other depressive symptoms.

Although the relationship between suicidal behaviour and depression have been extensively studied across the age span, little is known about gradations of suicidality as specified in the DSM-IV. Therefore, we examined the prevalence of recurrent thoughts of death, suicidal ideation, suicidal plans and suicide attempts in our sample and their relationship to various clinical characteristics of the MDD episodes.[19] Lifetime prevalence were the following: recurrent thoughts of death 67.5%, suicidal ideation 47.6%, suicidal plans 29.8% and suicide attempt 11.6%. For girls, all four suicidal behaviours tended to increase with age, while for boys none had significant differences across age groups. Suicidal youths were more severely depressed, showed more feelings of worthlessness and inappropriate guilt and showed a more distinct intensity of depressed mood. Suicide attempters were most likely to have a history of psychiatric hospitalisation. The highest prevalence of depressed mood was found in attempters (94.5%), followed by youths with suicide ideations (88%), recurrent thoughts of death (74.5%) and suicide plan (73.5%). Suicidal youths were more likely to evidence anxiety disorders and conduct disorder than non-suicidal peers. There were no differences in co-morbid disorders across various forms of suicidality. Depressed mood, psychomotor agitation, feelings of worthlessness, co-morbid anxiety and conduct disorder were independent and significant correlates of at least one form of suicidal behaviour. Worthlessness was the only symptom related to all four suicidal behaviours, which suggests that it may play a central role in increasing suicidality.

Although many (but not all) depressed youths exhibit some form of suicidal behaviour at some point in their lives, a logical further question is whether there are particular personality characteristics of depressed youths that increase the risk of suicidal behaviour. We explored this possibility[20] by examining the relationship between temperament and emotion self-regulation with DSM-specified suicidality.[13] Depressed non-suicidal and suicidal children had similar levels of negative emotionality. Non-suicidal children and children with recurrent thoughts of death were very similar on the four dimensions of temperament (emotionality, activity, sociability and shyness). Depressed children characterised by many maladaptive ways of regulating their own dysphoria were likely to have definite suicidal behaviours (ideation, plans or attempts). In contrast, a more extensive repertoire of adaptive regulatory responses to dysphoria signalled a decreased likelihood of specific suicidal behaviours. Youngsters who had attempted suicide had considerably higher maladaptive emotion regulation than other children. We detected interaction terms between emotion regulation and shyness as well as sociability for suicide attempters. These findings may suggest that when some temperament traits become extreme, emotion regulatory competence (or the lack thereof) has little impact on the odds of suicide attempt, but in the absence of extreme traits adaptive emotion regulation skills appear to serve as protective factors and lower the odds of attempted suicide.

As we noted above, about one-third of the children in our sample were rated by clinicians as having severe depression. Since depression severity has been implicated in the disorder's course and in treatment response, we examined whether early infant physiological characteristics could partly explain eventual MDD severity.[21] Specifically, we investigated whether peri-natal problems, developmental delay and difficult infant temperament render children vulnerable to earlier onset and more severe episodes of depression. However, we also took into consideration that the effects of risk factors may not be specific to MDD onset, but might also relate to the earliest internalising disorder (MDD, dysthymia or anxiety disorder). We found that difficult temperament predicted earlier onset of MDD and first internalising disorder, but its effect was ameliorated if the family was intact during early childhood. Its importance decreased as a function of age time. Peri-natal problems and developmental delay did not affect onset ages of disorders and none of the early childhood characteristics were associated with MDD episode severity. Difficult temperament was also associated with earlier dysthymia or anxiety disorder as well as MDD, indicating lack of specificity to MDD. Our findings highlight that even in a vulnerable sample, the putative negative effects of early infant characteristics are not immutable but can be ameliorated by family resources.

Another one of the enduring questions in the field has concerned the contribution of life events and stresses to childhood depression. Although we could not investigate causal relationships because our entire sample had MDD, we did examine developmental trends in life events and compared our sample's life event history with that of a comparison group of peers who we recruited from public schools.[22] The comparison sample included 724 children (399 girls); mean age was 10.8 years (SD 2.2 years). We queried both samples for 26 stressful life events. We examined both individual life events and five life-event groups (parental health, death, sociodemographic, intra-familial life events and a miscellaneous group containing abuse, teasing, police contact and suspension from school).

Depressed children experienced twice as many life events as the normative group. The number of life events increased with the age of the child in the normative group, while it was independent of age in the depressed group. Almost all individual life events were experienced significantly more often in the depressed group. Three life event groups increased the odds of MDD significantly: parental illness doubled the odds, intra-familial life events almost tripled the odds regardless of the child's age and death increased the odds by almost one-fifth. Repeated teasing and abuse increased the odds of MDD regardless of the age and gender of the child. Natural disaster, mother's serious somatic illness, father's psychiatric hospitalisation and the death of a close relative increased the chance of depression in children ≤11 years of age. Parental unemployment proved to be a risk factor in the older age group. Parental divorce increased the odds by five to 10 times in younger girls, but this effect decreased in older girls. Family arguments increased the chance of developing MDD with increasing age.

The association between mood disorders and certain risk behaviours such as smoking, drinking and drug abuse also deserves further attention.[23,24,25] We investigated these behaviours in a sample that, besides depressed probands, also included siblings with mood disorders.[26] MDD was present in 51%; the rest had minor depression, adjustment disorder or mood disorder not otherwise specified. The rate of co-morbid disorders were 76%. Thirty per cent had anxiety disorder, 18.4% had attention-defecit–hyperactivty disorder (ADHD), 14.7% had enuresis, 11.8% had tic disorder and 11% had dysthmia. The prevalence of smoking and drinking was 19.9 and 24%, respectively. The frequency of drug use was between 7 and 9.4% depending on the type of drug. Alcohol consumption was more frequent among girls. The presence of MDD increased the odds of drinking (odds ratio [OR] 2.7), while co-morbid anxiety disorder increased it further (OR 3.48). Generalised anxiety disorder and social phobia increased the odds most (OR 8.4 and 3.84, respectively). Co-morbid behavioural problems, most notably conduct disorder, enhanced the likelihood of smoking (OR 3.55).

It is unambiguous in the literature that physical illnesses reduce quality of life (QoL) in children. The effect of psychiatric illnesses was not extensively studied in this age group. Furthermore, few studies investigated parent–child agreement on children's quality of life. We compared mother- and child-reported QoL of the depressed sample with a group of non-depressed peers recruited from public schools.[27] Subjects of the comparison sample included 1,695 youngsters without clinically significant depressive symptoms. We refer to the original article for precise demographic characterisations of the samples.

QoL scores were lower in the depressed sample regardless of the reporter. Mothers of depressed children rated lower satisfaction for their children in the areas of school, family, peer relations and mental health than their offspring. Mothers of non-depressed children scored significantly higher on the QoL of all domains than their children. Presence of depression in the child decreased mother–child agreement, while older age had only a tendency for improved concordance. The total QoL scores of mothers and children correlated more closely in the non-depressed sample. Our results support the tendency of parents to relate more serious negative effects to depressive disorder than their children and to undervalue their non-depressed offspring's problems compared with non-depressed children.

As we noted previously, agreement is generally low to moderate between symptom reports of mothers and children, which might present as difficulty during the assessment process. Factors that influence individual reports and agreement have also been of interest.[28,29] We aimed to investigate and compare mother- and child-reported severity of child depressive symptoms.[30] Mothers reported higher symptom severity for boys, while parent-reported severity did not differ significantly from self-reports in girls. At the same time, girls endorsed significantly higher severities in self-reports than boys. Child-reported severity was associated with child sex, age and maternal depression and severity increased as girls got older. Mother-reported symptom severity increased with higher maternal depression scores; more educated mothers reported more severe cognitive symptoms for children and less severe vegetative symptoms for girls. Mother–child agreement was predicted only by the age of the child: older children and their mothers were more likely to agree than younger ones. Even though more depressed mothers reported more severe depressive symptoms in children, children of more depressed mothers themselves reported higher levels of mood symptoms for themselves, suggesting that they are at an increased risk of depression themselves.

The role of genetic deficits in the aetiology of childhood-onset mood disorders (COMD) is supported by compelling evidence. The genetic part of our study intended to replicate earlier findings and investigate new possibilities. Deficits in neural plasticity have been suggested to underlie the development of depression. The receptor neurotrophic tyrosine kinase B and its ligand, brain-derived neurotrophic factor (BDNF), play essential roles in neural plasticity. Messenger RNA (mRNA) expression of both of these genes has been shown to be influenced by stress and chronic antidepressant treatment. Markers in BDNF[31] and the neurotrophic tyrosine kinase receptor 3 (located on 15q25.3–q26.2, a region linked to early-onset mood disorders) were significantly associated with COMD in this sample;[32] however, the neurotrophic tyrosine kinase receptor 2 (NTRK2) was not.[33]

Results for cAMP-responsive element-binding protein (a transcription factor that increases the expression of key growth factors involved in synaptogenesis and neurogenesis) do not support previous evidence for this gene as a major factor contributing to depression.[34] Disturbances in stress hormones have been implicated in mood disorders, in particular in the hyperactivity of the hypothalamic–pituitary–adrenal axis (HPA). A G-protein-coupled receptor, vasopressin V1b, was found to be implicated in the aetiology of mood disorders, particularly in females.[35]

The existence of sex-specific aetiological factors in depressive disorders related to oestrogen was examined by genotyping 11 single nucleotide polymorphisms (SNPs) spanning the oestrogen receptor alpha gene. Three of the examined SNPs were found to be associated with COMD.[36] No evidence for association was observed with the adrenergic receptor genes (a1B, b3, a2C, a2A and b1) in this sample.[37] Genes involved in the regulation of inflammatory cytokine activity are considered to be strong candidates for involvement in genetic susceptibility to depressive disorder. Six key genes were tested (tumour necrosis factor [TNF], interleukin [IL]1A, IL1B, IL6, IL1RN and IL10); however, no association was observed.[38,39] Result of a genome scan using 405 microsatellite provided evidence for linkage with markers on two chromosomes (13q and Xq).[40] Within the 13q linkage region, we found suggestive evidence for association with markers in G72/G30,[41] genes previously associated with mood disorders. The gene for the X-linked orphan G-protein-coupled receptor in the X-linage region was not found to be associated with COMD.[42] No evidence of association was found between a functional polymorphism in the 5,10-methylenetetrahydrofolate reductase gene (MTHFR, an enzyme involved in the metabolism of folic acid) and COMD.[43] Polymorphisms in two serotonin receptor genes were investigated (HTR1B and HTR2A, and the serotonin transporter r SLC6A4) but no association was found with COMD.[44]

Conclusion

In this article we have summarised published findings from our study of the risk factors of childhood-onset depression (COMD). Knowledge of risk factors enables psychiatrists to pay special attention to vulnerable populations. By applying effective preventative methods early on, some of these disadvantages might be decreased and adoptive mechanisms initiated. It is important to imply and integrate the results of ongoing research into everyday practice. ■

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Please provide full details.

Depresszió vagy krónikus fáradtság szindróma?

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A krónikus fáradtság szindróma (Chronic Fatigue Syndrome-CFS) megosztja a szakembereket, különösen a klinikai definíciót és az etiopatogenezist illetően. A fáradtság a vezető tünet, amelyhez más fizikális és pszichológiai tünetek is kapcsolódnak. A tünetek hátterében kimutatható ok nem igazolható. A lányok gyakrabban betegszenek meg, mint a fiúk. Etiológiája nem tisztázott, valószínűleg multifaktoriális eredetű betegség, amelyben pszichológiai és családdinamikai faktoroknak is szerepe lehet. A terápia szempontjából leghatékonyabbnak a fokozatos fizikai és szellemi terhelés, és a CBT (cognitiv behavior terápia) mutatkozik. Számos kutató pszichiátriai betegségnek tartja.

KULCSSZAVAK: KRÓNIKUS FÁRADTSÁG SZINDRÓMA, MULTIFAKTORIÁLIS EREDET, FOKOZATOS TERHELÉS, CBT

A klinikai gyakorlatban gyakran találkozunk a fáradtságérzéssel, amely fizikai vagy szellemi megerőltetés következtében, de számos gyermekgyógyászati és gyermekpszichiátriai betegség tüneteként vagy gyógyszerek mellékhatásaként is kialakulhat. A krónikus fáradtság szindróma (Chronic Fatigue Syndrome-CFS) esetében ezzel szemben a háttérben kimutatható ok nem igazolható, és kis megerőltetés után is súlyos fáradtság jelentkezik, amelyen a pihenés nem segít. A krónikus fáradtság szindrómát 1988-ban írták le először, és annak ellenére, hogy az utóbbi két évtizedben több mint 2000 tudományos közlemény született vele kapcsolatban, jelenleg is megosztott a szakemberek álláspontja, különösen a klinikai definíciót és az etiopatogenezist, valamint a szindróma besorolását illetően, mind a gyermekek mind a felnőttek tekintetében. Nem tisztázott, hogy fizikális vagy mentális betegség-e, egyesek tagadják önálló kórképként való létezését. A pszichiátriai betegségek amerikai diagnosztikus rendszere, a DSM-IV nem tartalmazza a krónikus fáradtság szindrómát, míg az európai BNO-10 a neurotikus zavarok között, neurasthenia néven besorolja (1, 2). Ma a kutatók és a klinikusok is a fenomenológiával kapcsolatban azt a felfogást támogatják, amely jól elkülöníti a depressziótól és a szorongásos zavaroktól (15).
Definíciója olyan krónikus fáradtság, amely nem magyarázható sem fizikális, sem mentális betegséggel, és különböző fizikális tünetek kapcsolódnak hozzá. A krónikus fáradtság szindróma (CFS) elnevezést főként a klinikusok használják, a betegek jobban szeretik a myalgiás encephalomyelitis (ME) elnevezést, amely gyulladásra utal az agyban és a gerincvelőben, izomfájdalmakkal társulva, és kifejezi a betegség szomatikus jellegét. Magát a betegséget, myalgiás encephalomyelitis néven 1938-ban írták le először. 1988-ban vizsgálta az elnevezés legitimitását a UK Department of Health and Social Services és a British Medical Association, és megállapították, hogy a gyulladás nem vezetőtünet, valamint az izomfájdalom is sok esetben hiányzik. A betegség elnevezése máig nem egységes, számos elnevezés használatos ugyanarra a tünetcsoportra:

- 1988-tól használatos a név a Chronic Fatigue Syndrome (CFS): a Centers for Disease Control and Prevention vezette be az USA-ban. Azóta az Egyesült Királyságban és Kanadában is ezt az elnevezést használják.
- Chronic fatigue immune dysfunction syndrome: főként a biokémiai kutatók használják az Egyesült Királyságban, mert sokan azt gondolják, hogy a CFS pszichiátriai betegségre utal és ezáltal stigmatizál.
- Post-viral fatigue syndrome: a víruseredetre utal, azonban a különböző súlyosságú betegségek hátterében sem mindig igazolható a vírusinfekció.
- Krónikus Epstein–Barr-vírus vagy krónikus mononucleosis: virológusok vezették be az elnevezést, bár a betegség hátterében más vírusokat is kimutattak,

valamint krónikus fáradtság nélkül is megtalálták egészséges kontrollokban ugyanezeket a vírusokat.
- ✦ Low Natural Killer Cell Disease: ezt az elnevezést széles körben Japánban használják, arra utalva, hogy a kutatók a natural killer sejtek számának a csökkenését találták a betegségben.
- ✦ Yuppie Flu: beceneve a CFS-nek, pszichiátriai vagy pszichoszomatikus hátteret sejtetve.

Tekintettel arra, hogy a CFS gyakran fordul elő más mentális betegségekkel, valamint jellegzetes pszichés tünetei vannak, számos kutató pszichiátriai betegségnek tartja. Sokan úgy vélekednek, hogy a kórkép nem más, mint a major depresszió fizikális manifesztációja. Ezt támogatja, hogy depresszióban is gyakoriak a fizikális tünetek, valamint, hogy az antidepresszánsok sok esetben hatékonyak CFS-ben is. Ellentmond a fenti állításnak az, hogy számos esetben a betegek nem reagálnak antidepresszánsokra, és nincsenek depresszióra utaló vezető tünetek sem. A legnépszerűbb és legegyszerűbb az a felfogás, amely szerint olyan betegség, amely a tudatban zajlik (28).

A CFS egyre gyakrabban jelentkezik gyermek- és serdülőkorban, amelynek során csökken a beteg energiája és az aktivitási szintje, mély fáradtságérzés, erőtlenség, a reménytelenség érzése keríti hatalmába, növekszik a családtól való függőség, a társaktól és a természetes környezettől való izoláció. Gondosan megválasztott terápia mellett is nehéz a betegnek a betegséget megelőző szintű funkcionálását visszaállítani (28).

Diagnózis

Az epidemiológiai és klinikai kutatások szükségessé tették egy egységes definíció és kritériumrendszer kialakítását a krónikus fáradtság szindrómával kapcsolatban, amelyet az USA Centers for Disease Control and Prevention (CDC) hozott létre 1988-ban. Ezek a kritériumok nehezen voltak használhatóak a klinikumban, ezért 1993-ban módosították az eredeti definíciót és kritériumokat. Jelenleg a britt Oxford Kritériumok vagy a Fukuda CDC (USA) Kritériumok alapján diagnosztizáljuk a krónikus fáradtság szindrómát. A két kritériumrendszer meglehetősen hasonlít, az amerikai (CDC) diagnózis inkább a szomatikus tünetekre, míg az angol (Oxford) diagnózis a mentális fáradtságra helyezi a hangsúlyt. A gyermekek és serdülők diagnosztikája megegyezik a felnőttek diagnosztikus kritériumaival.

Oxford-kritériumok

A fáradtság, a vezető tünet, amely súlyosan károsítja az affektív a fizikális és a mentális funkciókat. A fáradtság legalább 6 hónapig fennáll, és az idő több mint 50%-ában jelen van, nem folyamatos megerőltetés következménye, és a pihenés nem csökkenti. Más szimptómák is, mint a myalgia, hangulat és alvási problémák is kapcsolódnak a fáradtsághoz, amelynek hátterében, ha azonosított betegség van, kizárja a fáradtság szindrómát. A krónikus fáradtság kialakulását gyakran megelőzi egy fizikális betegség, amely az esetek többségében vírusfertőzés. Szkizofrénia, affektív betegség, pszichoaktív szer használata, evészavar vagy organikus agyi betegség jelenléte kizárja a diagnózist.

A CDC diagnosztikus kritériumok

Kizárják a kezeletlen hypothyreoidismust, az alvási apnoet a narkolepsziát, és a súlyos obesitast (BMI>45), és az alábbi tünetek közül legalább 4 fennáll:
- ✦ diffúz izomfájdalom, izomgyengeség, több ízületben jelentkező, változó lokalizációjú arthralgia, látható eltérés nélkül,
- ✦ alvászavar, amely kevésbé hatékony alvást jelent, lehet inszomnia és hiperszomnia is,
- ✦ a kognitív funkciók, elsősorban a koncentrációs készség romlása,
- ✦ enyhe láz, torokfájás, tapintható, nyomásérzékeny nyirokcsomók,
- ✦ korábban nem tapasztalt jellegű fejfájás.

Előfordulhatnak még: vizuális scotomák, fotofóbia, feledékenység, kineziofóbia (irracionális félelem a mozgástól), vegetatív labilitás. Jellemző, hogy a betegek egyszerre csak egy dologra tudnak figyelni, gondolkodásukat meglassultnak érzik (13).

A diagnosztikus kritériumok megalkotása fontos volt a CFS területén zajló kutatások és klinikai gyakorlat összehasonlíthatósága szempontjából. A kritériumokat kutatási céllal alakították ki, a klinikai gyakorlatban is használhatóak, bár gyermekek esetében a 6 hónapos minimum időtartam túl hosszúnak tűnik (15).

Epidemiológia

A betegség előfordulását illetően iskolákban, és a gyermekorvosi alapellátásban végeztek felméréseket. Az USA-ban, nem a CFS szigorú kritériumainak megfelelő, de CFS-szerű tünetek a gyermek- és serdülő átlagpopulációban 2%-ban fordulnak elő (19). Angliában a megkérdezett gyermekek és serdülők 32%-a panaszkodott aktuálisan fáradtságról, 0,6% volt krónikusan fáradt, és 0,19% megfelelt a CFS diagnosztikus kritériumainak (9). A lányok gyakrabban betegszenek meg, mint a fiúk, hasonlóan major depresszióban is a serdülőlányok kétszer gyakrabban betegszenek meg, mint fiú kortársaik (4).

Viner és Hotopf által végzett vizsgálatban a 16.567 résztvevő gyermek 0,8%-ánál diagnosztizáltak CFS-t. A legnagyobb rizikót a női nem és a magasabb szociális osztályhoz való tartozás gyermekkorban, jelentette. Az anya pszichológiai problémája vagy betegsége gyermekkorban, a születési súly, atópia, obesitas, az iskolából kimaradás, szülők betegsége nem jelentett kockázatot a betegség kialakulása szempontjából (35).

Etiopatogenezis

A gyermekek és serdülők krónikus fáradtság szindrómájának etiológiája nem tisztázott, valószínűleg multifaktoriális eredetű betegség, amelyben pszichológiai és

család dinamikai faktoroknak is szerepe lehet. A betegség kialakulásához hozzájárulnak külső ágensek, például a vírusok, és a betegséget megelőző aktív életstílus.

Infekciók

Tekintettel a tünetekre és arra, hogy az anamnézisben gyakran előzi meg a betegséget vírusfertőzés, valamint a lefolyásra (remisszió-exacerbáció), elsőként a látens vírus reaktiváció gyanúja merült fel, mint oki tényező. Egy korábbi elnevezés volt ebből adódóan a posztvirális szindróma. A vírusfertőzésekkel kapcsolatban felmerült egy másik elmélet is, amely szerint az akut vírusfertőzés diszregulálja az immunapparátust, amely az NK (natural killer) sejtek aktivációján keresztül vezet a tünetek kialakulásához (12). Számos vírus került szóba kóroki tényezőként: Epstein–Barr-vírus, influenzavírus, citomegalovírus, Coxakie-B, adenovírus, herpesvírus, hepatitis-C vírus. A vizsgálatok hosszú listája ellenére nincsenek specifikus laboratóriumi markerek, a szubjektíve markáns tünetek, és ezekkel összhangba nem hozható fizikális és laboratóriumi eltérések hiánya felvetette annak lehetőségét, hogy a CFS pszichológiai probléma (18).

Endokrin rendszer

A hypothalamus-hipofízis-mellékvesekéreg tengely (HPA-axis) enyhe hipofunkcióját írták le a kutatók krónikus fáradtság szindrómában. Ez az eltérés azonban nem egyértelmű, mert oka és következménye egyaránt lehet a kórképnek. A kutatások biztosabban azt támasztják alá, hogy multifaktoriális eredete van a betegségnek, de a HPA-tengelynek biztosan van szerepe a tünetek exacerbációjában és perzisztálásában (24).

Neurotranszmitterek

A szerotonin szerepe a hangulatzavarok és a szorongásos kórképek esetében már igazolt. Számos folyamatban játszik szerepet, többek között emeli a szérum prolaktinszintjét. A szelektív szerotonin reuptake-gátló (SSRI) antidepresszánsok alkalmazásakor emelkedik a plazma prolaktinszintje. A krónikus fáradtság szindrómában szenvedők esetében a prolaktinszint-emelkedés kifejezettebb, mint az egészséges kontrollok esetében, míg depressziósok esetében a prolaktinszint nem emelkedik, sőt egyes esetekben csökken (30). Ezek alapján feltételezzük, hogy a krónikus fáradtság szindrómában szenvedők szerotonin receptorai túlérzékenyek, valamint, hogy ugyan a szerototnin szerepet játszik mind a krónikus fáradtság szindróma, mind a depresszió patogenezisében, de nem valószínű, hogy a két betegségnek közös lenne a patofiziológiája. A krónikus fáradtság szindrómás betegek estében az emelkedett agyi szerotoninaktivitás adhatja a nagyfokú fáradtságérzést, míg a vele párhuzamosan megemelkedett prolaktinszint a járulékos tünetek egy részéért lehet a felelős.

Az, hogy a krónikus fáradtság szindrómában szenvedő betegek esetében szerotonin ellenes antitesteket sikerült kimutatni és ezeket az antitesteket a betegek családtagjainál is megtalálták a betegség genetikai prediszpozíciójára irányítja a figyelmet (20).

Immunrendszer

A krónikus fáradtság szindrómás betegek esetében krónikus immunaktiváció áll fenn, csökkent NK és fokozott T-sejt aktivációval, a cirkuláló citokinek felszaporodásával. A krónikusan aktivált állapot krónikus antigénexpozíció következménye lehet. Az antigének lehetnek exogének, például vírusok vagy endogének, mint például az autoantigének. Felmerül annak a lehetősége is, hogy az immunrendszer és a neuroendokrin rendszer együttesen oka a betegségnek (22).

Genetika

Családvizsgálatok a genetikai hátteret támasztják alá. Monozigóta ikrek között a konkordancia aránya 55%, heterozigóták esetében 19%. Valószínűsíthető, hogy a genetikai vulnerabilitás és környezeti tényezők együtt határozzák meg a betegséget. Egyes kutatók úgy gondolják, hogy vannak olyan családok, amelyekben genetikusan kódolt immunológiai eltérés, nevezetesen NK-sejt-diszfunkció érzékenyít a krónikus fáradtság szindrómára (5).

Az amerikai CDC, eddigi legnagyobb vizsgálatában, a CFS Computational Challenge (C3), a kutatók telefonos interjú alapján választották ki a 227 krónikus fáradtság szindrómában szenvedő beteget és az egészséges kontrollokat.

A vérmintákból, mintegy 20.000 gén aktivitását határozták meg, majd számítógépes algoritmusok segítségével próbálták megfejteni, hogy mely génszekvenciák hozhatók összefüggésbe a tünetekkel. Úgy tűnik, hogy a krónikus fáradtság szindrómában szenvedők bizonyos, a stresszválaszban szerepet játszó fehérjéket, receptorokat, vagy neurotranszmittereket kódoló génjei jellegzetes polimorfizmust mutatnak, azaz szekvenciájuk eltér az egészségesekétől. Körülbelül 50 gént és 500 polimorfizmust fedeztek fel, amelyek a kórképben felelős hypothalamus-hipofízis-mellékvesekéreg tengelyt befolyásolhatják. A glükokortikoid-receptorok, a MAO-A és -B, valamint a triptofánhidroxiláz génjeinek szerepe kiemelkedő. Ezek az eredmények lehetővé tehetik a krónikus fáradtság szindrómában szenvedő betegek elkülönítését az egészségesektől, a gének célzott vizsgálatával, ezáltal 75% valószínűséggel kimondható lehetne valakiről, hogy tünetei hátterében CFS áll-e (34).

A londoni St George Egyetem kutatói 47.000 gén polimorfizmusát vizsgálták meg, és 100 gén expressziójában igazoltak eltéréseket az egészségesekhez képest. Ezen gének nagyrésze az immunrendszerrel áll kapcsolatban, bár a betegek közötti génexpressziós mintázat nagy eltéréseket mutat. A továbbiakban béta-interferon klinikai alkalmazását tervezik a CFS-es betegeknél, mert ha a tünetek kiváltásában a vírusok szerepét feltételezzük, a béta-interferon az infekció felszámolásával a tartós gyógyulást jelentheti (34).

Egyéb tényezők

OXIDATÍV STRESSZEK

Krónikus fáradtság szindrómások esetében az oxidatív stressz, amelyet a felszaporodó szabad gyökök okoznak, és az antioxidáns védelem közötti egyensúly zavarát találták a kutatók, de ez a mechanizmus napjainkban még tisztázatlan (10).

FÉMEK

A krónikus fáradtság szindrómában szenvedőknél a szérum alumíniumszintet magasabbnak, míg a szérum vasszintet alacsonyabbnak találták, mint egészségesekben.

DISZAUTONOMIÁK

A CFS szoros kapcsolatban áll a vegetatív idegrendszer eltéréseivel, a szimpatikus-paraszimpatikus egyensúly szimpatikus irányba tolódik el. A kutatók egy része a diszautonomiák közé sorolja a krónikus fáradtság szindrómát, ezek olyan betegségeket foglalnak magukba, amelyek az autonóm idegrendszer-működés változásán alapulnak. Ilyen a krónikus ortosztatikus intolerancia, amely serdülőlányok körében gyakran előforduló eltérés. Ez esetben az ortosztatikus tenzióesés késleltetett. 15–45 éves nők körében gyakori és a krónikus fáradtság szindrómás betegek esetében kétszer gyakrabban fordul elő (32).

IGY PATOLÓGIAI ELTÉRÉSEK

Ausztrál kutatók (2006) Epstein–Barr-fertőzés után vizsgáltak meg 39 beteget. A fertőzést követő 6 hónap múlva 31 beteg tünetmentes volt, míg 8 betegnél CFS alakult ki. Nem volt jelentős eltérés a két csoport vírusterhelésében vagy immunválaszaiban, ezért nem lehet a szokásostól eltérő teljes testi immunreakcióval magyarázni a krónikus fáradtság kialakulását, és a tünetegyüttest nem az elhúzódó fertőzés okozta. Azt feltételezik, hogy a tüneteket a vírusfertőzés által közvetve okozott agysérülés okozza, ugyanis a vírusok aktiválják az agy immunrendszerének részét képező mikroglia sejteket, amelyek lázas állapothoz hasonló tüneteket okoznak. A fertőzés során megsérülnek az agyi mikroglia sejtek, ezzel megváltozik az agy fájdalomkezelő mechanizmusa. A betegek fáradtsága inkább agyi, mint testi eredetű. Ezzel magyarázható, hogy például influenza után fájdalom, álmosság, levertség, fáradtság marad fenn a fertőzésből való gyógyulás után is. Állatkísérletek bizonyítják, hogy az immunrendszert ért támadások hetekig aktív állapotban tartják az agyi mikroglia sejteket (34).

A patofiziológiával kapcsolatban a kutatási eredmények megerősítik a központi idegrendszer szerepét, a fokozott szerotonerg aktivitást, a hypothalamus-hipofízis-mellékvesekéreg tengely alulműködését. A kérdés továbbra is az, hogy ezek az elváltozások okai vagy következményei-e a krónikus fáradtság szindrómának? Az immunrendszer szerepe biztos alapokon nyugszik, de a specifikus mechanizmusokra vonatkozó adatok egyelőre ellentmondásosak. A kutatások arra utalnak, hogy a betegség részben genetikai eredetű, de a környezeti hatások döntő jelentőségűek (11). Az, hogy a CFS patofiziológiai hátterével kapcsolatban az eredmények sokfélék, és gyakran ellentmondásosak, felveti annak a lehetőségét, hogy egy klinikailag heterogén betegségcsoporttal állunk szemben (3).

Klinikai jellemzők

Az esetek többségében akut megfázás, vagy vírusinfekció tüneteivel kezdődik, de kialakulhat fokozatosan is. A diagnózis akkor állítható fel, amikor a fáradtság központi problémává válik. Gyermekek esetében jellemző, hogy súlyos a fáradtság és a fejfájás, gyakran panaszkodnak megszakított alvásról, de hiperszomnia is előfordul főként serdülők esetében (15). Gyermekek esetében a fáradtság igen kifejezett lehet, gyakran érzik úgy, hogy nem tudnak délnél hamarabb felkelni, és a nap folyamán többször van szükségük pihenő időszakokra. A fáradtság váltakozhat rövid időtartamú aktív időszakokkal. Az iskolába járást gyakran felfüggesztik, és megszűnnek kortárskapcsolataik. A fáradtság miatti funkciókárosodás nagyobb mértékű, mint más gyermekgyógyászati vagy gyermekpszichiátriai betegségeknél, amelyek fáradtsággal járnak. Súlyos esetekben az izomzat atrofizál, tolószékben vagy ágyhoz kötve élnek a krónikus fáradtság szindrómában szenvedő gyermekek. Ez komoly gondot okoz a családnak. Oly mértékben fordulnak a beteg gyermek felé, amely a család aktivitását is lecsökkenti, a családi élet a beteg gyermek körül forog, a gyermekek dependensen kapcsolódnak a szülőkhöz, elsősorban az anyához (15).

Diagnózis/Differenciáldiagnózis

A diagnózist részletes kivizsgálásnak kell megelőzni. Az anamnézist mind a gyermekektől, mind szüleiktől szükséges felvenni, mert azok a vizsgálatok, amelyek a szülők és a gyermekek értékelését hasonlítják össze, azt találták, hogy a szülők és gyermekeik értékelése között jelentős különbségek vannak a gyermek tüneteit illetően. A szülők csak 0,04%-ban ismerték fel gyermekeiknél a betegséget, és a gyerekek által említett tünetekkel szinte nem volt átfedés (9). A részletes orvosi vizsgálatnak tartalmaznia kell a vérkeringési és vérképző rendszer, a mononucleosis indikátorok, a máj-vesefunkció, a pajzsmirigy vizsgálatát, fejfájás és izomfájdalmak esetén neurológiai kivizsgálást. Amennyiben ismétlődő fertőzések szerepelnek az anamnézisben, a teljes immunstátusz vizsgálata szükséges. A gyermekpszichiátriai kivizsgálás fontosságát hangsúlyozza a szakirodalom, hiszen számos gyermekpszichiátriai kórkép mutathat hasonló tüneteket (15).

Kevés olyan vizsgálat van, amely a gyermekkori CFS jellegzetességeit vizsgálja, de még kevesebb, amely a krónikus fáradtság szindrómában szenvedő gyermekeket hasonlítja össze az emocionális zavarban szenvedő gyermekekkel. A krónikus fáradtság szindrómás gyermekekkel végzett vizsgálatok kis mintákon és klinikailag he-

terogén betegcsoportokon történtek (pl. a komorbiditások szempontjából). Ezen összehasonlító vizsgálatok alapján sikerült sok szomatikus tünetet azonosítani, míg kevés a depresszióra jellemző vezető tünet, mint harag, irritált viselkedés, depresszív hangulat, a depressziós fiatalokkal összehasonlítva (6, 7, 17, 29). A major depresszió az amerikai diagnosztikus rendszer (DSM-IV) szerinti kritériumai a következők: depresszív hangulat, amelyet gyermekeknél és serdülőknél helyettesíthet ingerlékenység, irritabilitás és/vagy anhedonia (az öröm érzés elvesztése a korábban örömteli tevékenységekkel kapcsolatban), amelyek kötelező tünetei a depressziónak. Mellettük étvágyváltozás, alvásproblémák, pszichomotoros aktivitás változása, fáradtság, alacsony önértékelés/önvádlás, koncentrációs nehézségek, szuicid gondolat/terv/kísériet lehet jelen. A kötelező tünetek közül legalább az egyiknek jelen kell lennie legalább két héten keresztül, és ezzel egy időben legalább még 4 további tünetnek ugyanabban a legalább 2 hetes időszakban.
Míg a depresszió esetében a kötelező hangulati tünetek közül egy jelenléte elengedhetetlen, addig ezek jelenlétére nincs szükség a CFS diagnózisához. A két betegség esetében a fáradtság és a koncentrációs problémák, valamint a pszichomotoros gátoltság terén van átfedés. Mindkét esetben a tünetek jelentős mértékben rontják a funkcionálást. A különbség a tünetek fennállásának időkritériumában vannak. Míg depresszió esetében elegendő a 2 hetes időtartam, addig a CFS esetében a tünetek 6 hónapig kell, hogy jelen legyenek. Ha figyelembe vesszük, hogy a depressziós epizódok átlagos időtartama gyermek- és serdülőkorban 7-9 hónap, akkor látható, hogy az időkritérium csekély mértékben segíti a differenciáldiagnosztikus munkát (21). Ráadásul CFS-es gyermekek esetében a 6 hónapos időtartamot a kutatók túl hosszúnak tartják (15).
A gyermekkori depresszió gyakran jár együtt szomatikus tünetekkel, mint fejfájás, hasfájás, izomfájdalmak, végtagfájdalmak (16). Ezek további átfedést jelentenek a CFS-sel. Ezen szomatikus tünetek a szorongásos zavarok között is gyakoriak, ráadásul ebben a betegségcsoportban szintén gyakori a fáradtság előfordulása. Kiemelendő a szeparációs szorongás, amely esetben a gyermek elutasítja az iskolába járást, de ennek hátterében nem a fáradtság áll, hanem a számára fontos személytől, leggyakrabban az édesanyától, való elválási nehézség/képtelenség. A gyermek- és serdülőkori CFS-ben gyakori az étvágyváltozás és a fogyás. Fontos elkülöníteni az anorexia nervosatól, amely betegség esetében szintén a testsúlyvesztés van előtérben, és gyakrabban fordul elő lányoknál, de a fogyás hátterében intenzív, megszorító diéta, olykor extrém mennyiségű testmozgás és testképzavar áll.

Komorbiditások

Komorbid szorongásos és depresszív zavarok a CFS-ben szenvedő gyermekek felében-háromnegyedében fordul elő (6, 14). Egy vizsgálatban 15 CFS-ben szenvedő gyermek közül 5 esetben teljesültek a major depresszió kritériumai, egy másik vizsgálatban a CFS-ben szenvedő serdülők és kontroll krónikus testi betegségben szenvedők csoportját összehasonlítva a mentális és fizikai fáradtság valamint a depresszió egyidejű jelenléte szignifikánsan gyakoribb volt a CFS-es csoportnál (31, 36).
Garralda és munkatársai (2005) összehasonlító vizsgálatában 28 CFS-ben szenvedő gyermeket hasonlított össze 27 emocionális zavarban (ED, amely a depressziót és szorongásos zavarokat foglalta magába) szenvedő gyermekkel. Eredményeik azt mutatták, hogy a CFS-ben szenvedő gyermekek körében alacsony a premorbid pszichopatológiai eltérések aránya, viszont magas az emocionális betegségek komorbiditása. Az életkorral nő a CFS-es betegekben a pszichopatológiai eltérések prevalenciája, és a CFS gyógyulása után is megmaradnak az emocionális tünetek. Az emocionális betegségek gyakori jelenléte a CFS-es gyermekekben, és az alacsony premorbid emocionális eltérések azt jelenthetik, hogy a CFS-ben szenvedő betegek pszichopatológiai eltérései reaktívak. Személyiség problémák mindkét csoportban magas arányban fordultak elő, amely megemeli annak a valószínűségét, hogy CFS-ben pszichológiai betegségek is jelen legyenek (15).

Egyéb pszichológiai jellemzők

Carter és munkatársai (1995) vizsgálatukban a CFS-es, depressziós és egészséges kontrollgyermekek csoportját hasonlították össze. A CFS-ben szenvedő gyermekek fehérek voltak többségükben, és a közepes-magas szocio-ökonomiai státus jellemezte őket. A korai serdülő éveikben lévő lányok hajlamosabbak voltak a CFS-re. A Gyermek Depresszió Kérdőíven (CDI, Child Depression Inventory) alacsonyabb pontszámot töltöttek ki a depressziós csoporthoz képest, kivéve a CDI Anhedonia alskáláját, amely az örömtelenséget a szokásos tevékenységek során, az alvási problémákat és az étvágy megváltozását jelzi. Ezzel szemben kevésbé jelezték a negatív hangulatot, az önértékelési problémákat, amelyek a depressziós gyermekek és serdülők vezető tünetei voltak. A CFS-esek szignifikánsan több szomatikus tünetet említettek a másik két csoporthoz viszonyítva. A CFS-ben szenvedő gyermekek életminőségében kiemelkedően nagy változást jelentett a betegség, amely magába foglalta az iskolai teljesítményt, az iskolán kívüli aktivitást, a szociális interakciókat, és szignifikánsan magasabb volt a szintje a pszichostresszeknek. Az életminőség-változás hasonló volt a depressziós csoport életminőség változásához. Az egészséges kontrollokkal összehasonlítva, a CFS-esek között gyakrabban fordult elő visszahúzódó viselkedés, a szociális kapcsolatok nehezítettsége, figyelem koncentrációs zavar, internalizáció. A CFS-es gyerekek és az egészséges kontrollok depresszív szimptómáinak az analízise során nem volt jelentős különbség. A fizikális és laboratóriumi vizsgálat nem hozott értékelhető eredményt a 3 csoport összeha-

sonlításában. A tanulmány utal arra, hogy a magas szocio-ökonómiai státus műtermék lehet, mert ezek a családok valószínűleg gyakrabban viszik gyermekeiket szakorvoshoz a fáradtság tüneteivel (6).
A CFS-es serdülőknél az egészséges kontrollokhoz képest szignifikánsan gyakoribb a problémás személyiségvonás vagy a személyiségzavar. Jellemző személyiségvonások a lelkiismeretesség, érzékenység, értéktelenség érzés, emocionális labilitás, fontoskodás, perfekcionizmus, fokozott gyanakvás, zárkózottság. A személyiségbeli nehézségek és a személyiségzavar szignifikánsan gyakrabban kapcsolódott pszichológiai tünetekkel és csökkent szociális készségekkel a CFS-ben szenvedő serdülők körében, de azok megkülönböztethetőek voltak az epizodikus pszichiátriai betegségektől (15, 26, 6).
Middendorp és munkatársai (2001) a krónikus fáradtságban szenvedő serdülő lányok pszichoszociális alkalmazkodásának vizsgálata során adekvátnak találták a lányok önértékelését, és szociális képességeit, optimista és áthidaló megküzdési stratégiákat alkalmaztak és pozitív életszemléletük volt, ezzel szemben alacsony volt a kompetenciájuk a serdülő-specifikus feladatokban. Ezek a megküzdési stratégiák a terápia során segítik a CFS-ben használatos rehabilitációs programokat (23).

Életesemények

A gyermekkori életesemények és a CFS közötti kapcsolat vizsgálata során azt a következtetést vonták le a kutatók, hogy elsősorban a korábbi szexuális abuzusok, gyakran vezetnek krónikus fáradtság szindrómához fiatal felnőttkorban (33).
Viner és Hotopf (2004) birth cohort vizsgálata során 16.567 újszülött életútját követte végig. Azt a megdöbbentő eredményt találták, hogy azok a gyerekek, akik 10 éves koruk körül nem sportoltak rendszeresen, kétszer gyakrabban betegedtek meg felnőtt korukban CFS-ben (35).

Családi jellemzők

A CFS-es gyermekek és serdülők családi jellemzőit az emocionális zavarban (ED) szenvedők családi jellemzőivel összehasonlítva, a CFS-csoport családjaiban a betegség kezdete előtt a szülőknek több fizikális betegsége és infekciója volt, míg az ED csoportban a szülőknek gyakrabban volt a betegség kialakulását megelőzően pszichológiai problémájuk. Ezzel szemben a szülők emocionális betegsége és mentális distressz szintje magasabb volt a CFS-es gyermekek csoportjában, mint más gyermekgyógyászati betegségben szenvedők szüleinek körében (15). A CFS-ben szenvedő gyermekek családjában jellemző, hogy a családtagok a szomatikus tüneteket megerősítik, meggyőződésük, hogy a tüneteket testi betegség okozza. Ez hasonló számos más mentális betegség esetében tapasztalt családi attitűdhöz. A CFS-ben szenvedő gyermekek esetében gyakori, hogy a szülőknek is hasonló tüneteik vannak. Jellemző rájuk, hogy nehézségekkel szembekerülve szomatikus tüneteket produkálnak, a problémák megoldásában a segítségkérés ritka 828).

Gyógyulás

Az enyhe esetekről keveset tudunk, mert nem kerülnek szakemberhez. A szakorvosi ellátásban részesülőknek fele-háromnegyede teljesen meggyógyul. Azokban az esetekben, amikor az iskolába járás elutasítása is jelen van, a gyógyulás általában elhúzódó, 1 évnél is hosszabb lehet, de sok esetben a gyógyulás 3 évet is igénybe vehet (27).

Terápia

Whiting és munkatársai 2001-ben részletes elemzést tettek közzé a CFS kezelésével, és a betegek gondozásával kapcsolatban. A cikk megjelenését a szakemberek közötti, a CFS hatékony kezelését érintő vita inspirálta. 19 speciális adatbázis tudományos közleményeit dolgozták fel, végül az összehasonlíthatósági feltételeknek megfelelő 44 cikk adataira támaszkodtak munkájuk során. A leghatékonyabbnak a fokozatos terhelést, és a CBT-t (cognitiv behavior therapy) találták, míg az immunglobulin és hidrokortizon kezelés kevésbé volt hatékony. Egyéb gyógyszeres és alternatív kezelésekről kevés adat állt rendelkezésükre ahhoz, hogy egyértelmű következtetéseket vonhassanak le. A tünetek azt feltételeznék, hogy a pihenés hozza meg a javulást, ezzel szemben az aktivitás csökkentése az elhúzódó lefolyást eredményezte (37).
Gyógyszeres kezeléssel kapcsolatban csupán egyetlen placebokontrollált randomizált vizsgálat áll rendelkezésünkre gyermekek körében. A gamma-globulin infúziót hatásosnak találták CFS-ben gyermekek esetében, ennek ellenére nem vált rutin klinikai gyakorlattá.
Felnőttek esetében az antidepresszánsokat találták hatékonynak, különösen, ha depresszió is kapcsolódott a CFS-hez. Számos próbálkozás történt még acyclovirrel, bétareceptor-blokkolókkal, acetilkolinészteráz-bénítókkal, amelyek bizonyítottan hatástalanok maradtak. NADH-val, magnéziummal, L-karnitinnal, végzett kezelések hatása kétséges, további vizsgálatok szükségesek. Kísérleti stádiumban van az aferezis és a kezelt, saját nyirokcsomósejtek visszaadása.
Powell és munkatársai (2001) végeztek vizsgálatot azzal kapcsolatban, hogy hatékony-e a CFS-ben szenvedő betegek fokozatos terhelése és edukációja, amelynek során megmagyarázzák a tüneteket, és fokozatos testmozgásra ösztönzik őket. A CFS Oxford kritériumainak megfelelő 148 felnőtt CFS-es beteget választottak be a vizsgálatba. Véletlenszerűen osztották a betegeket 4 csoportba. A kontrollcsoport csak hagyományos terápiában részesült, a minimál intervenciós csoportban két

egyéni beszélgetésben részesültek a betegek a tüneteiket illetően, valamint két alkalommal telefonhívással követték őket. Kaptak egy átfogó képzési csomagot, és fokozatos otthoni testmozgásra ösztönözték őket. A telefonintervenciós csoport tagjai a minimál intervenciós csoporthoz képest még további két telefonhívást kaptak, míg a maximális intervenciós csoport tagjai ezen felül még további 4 hónapon keresztül további hét személyes megbeszélésen vettek részt. 12 hónap elteltével a fizikális állapotot értékelték. Az intervenciós csoportokból 79 betegnél találtak kielégítő eredményt, míg a kontrollcsoportban csak 2 betegnél. Ez a különbség statisztikailag szignifikáns, azonban a 3 intervenciós csoport között nem találtak szignifikáns különbséget a tünetcsökkentő hatékonyságot illetően. A szerzők hangsúlyozzák, hogy tekintettel arra, hogy mivel a CFS többnyire testi tünetekből áll, a betegek orvosi tájékoztatatás híján testi betegségnek tulajdonítják, amely a rossz prognózis egyik záloga (25).

CFS-es gyermekek esetében a kognitív behavior terápia hatékonyságát a vizsgálatok is igazolták. Ennek során a terápiás terv elkészítéséhez szükséges a szimptómák pontos leírása és a viselkedés analízise az iskola az otthon és a szociális területek függvényében. Részletes felmérés szükséges az alvás, az aktivitás és a pihenés minőségét és mennyiségét illetően. Fontos a napi energiaszint-ingadozás monitorozásához energianapló vezetése, valamint a fáradtság számszerűsítése. Az energiaszint napi ingadozásához mérten aktivitási ütemtervet kell készíteni. A legalacsonyabb energiaszintű napszakokra lazítást, pihenést javasolnak, míg az energiával telítettebb időszakokra a figyelmet és kognitív-, valamint intenzív fizikai teljesítményt igénylő feladatokat. A cél, hogy minél kevesebb időt töltsön ágyban alvás nélkül a beteg. A fokozatos fizikai terhelés, az alvás higiéné (meghatározott időben történjen az elalvás és a felébredés) kialakítása, valamint a negatív kogníciók felismerése és helyettük alternatív magyarázatok adása jelenti a terápia fő irányvonalát. Az aktivitás formájának a sétát vagy a kerékpározást ajánlják (15). *Chalder és munkatársai* (2002) családra fókuszált kognitív terápiáról számoltak be CFS-ben szenvedő gyermekek és serdülők esetében. A családokkal 2 hetente találkoztak, és 1 évig követték őket. A cél a gyermek iskolába való visszatérése volt. Ehhez a fokozatos terhelést, az alvásrendezést, valamint a negatív kogníciók pozitívba fordítását alkalmazták. Mindezekhez igénybe vették a szülők aktív segítségét. A szülőknek elmagyarázták a helyes attitűdöt a betegséggel kapcsolatban, amellyel segíthetik gyermekük gyógyulását. Felkészítették a családokat az esetleges remisszióra (8).

Mindezek azt sejtetik, hogy a magatartási intervenciók a családi megközelítéssel összehangolva hatásos terápiát jelenthetnek. A leírt eredmények korlátja, hogy nincsenek randomizált kontrollált vizsgálatok, amelyek ennek a megközelítésnek a hatásosságát igazolnák gyermekek esetében. Jelenleg két serdülőkkel történő randomizált, kontrollált vizsgálat van folyamatban.

A tapasztalat szerint a gyermekek és családjuk számára kulcsfontosságú az a feltevés, hogy fizikális betegséggel állnak szemben, ezért fontos a részletes és szakszerű felvilágosítás és a folyamatos orvosi támogatás.

Következtetések

A CFS-ben szenvedő gyermekekkel és serdülőkkel kapcsolatban lassan gyűlnek a tények. Fontos a precíz, körültekintő diagnosztikus protokollok alkalmazása, mind gyermekgyógyászati, mind gyermekpszichiátriai szempontból. Jelenleg ellentmondásos a CFS megítélése a szakemberek körében annak tekintetében, hogy fizikális vagy pszichés betegségnek tekinthető a kórkép. Számos átfedés van a CFS és az emocionális betegségek között gyermek- és serdülőkorban, azonban vannak specifikus különbségek, mind a tünettanban, mind a vulnerabilitásban.

A rehabilitációs program a családi kognitív behavior terápián alapul, amely jól alkalmazható és hatékony. A terápia hatékonyságának szempontjából a család felvilágosítása és bevonása a gyermek kezelésébe, a siker egyik záloga.

SUMMARY

Depression or chronic fatigue syndrome?

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There is no clean consensus among experts regarding Chronic Fatigue Syndrome (CFS), especially in clinical definition and etiopathogenesis. Fatigue is the leading symptom and other physical and psychological symptoms may be associated with it. There is no exact cause in the background of the symptoms. Girls are more frequently affected than boys. Etiology is not clear, possibly it is a multifactorial disease, where psychological and family dynamics may have a role. In therapy, gradual activity and cognitive behavioral therapy (CBT) are the most effective. Several researchers asses it as a psychiatric disease.

Key words: chronic fatigue syndrome, multifactorial origin, gradual activity, CBT

AZ IRODALOMJEGYZÉK A SZERZŐ CÍMÉN ELÉRHETŐ.

Köszönetnyilvánítás

Szeretnék köszönetet mondani témavezetőmnek Dr. Vetró Ágnesnek, hogy munkám végzésében mindvégig támogatott, folyamatos szakmai segítséget nyújtott számomra.

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Külön köszönettel tartozom Benák Istvánnak az adatok kezelése során nyújtott folyamatos segítségéért.

Szeretném megköszönni Dr. Boda Krisztinának, Skultéti Dórának, Kovács Eszternek, Georges Charles-nak a statisztikai elemzések elkészítését.

Köszönet illeti a Gyermekkori kezdetű depresszió munkacsoport tagjait a kutatás különböző fázisainak szervezéséért és lebonyolításáért, és a kutatásban résztvevő családokat az együttműködésért.

Végül, de nem utolsó sorban, szeretném megköszönni férjemnek, lányaimnak és szüleimnek folyamatos segítségüket, támogatásukat és megértésüket.