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Early-onset schizophrenia as a progressive-deteriorating developmental disorder: evidence from child psychiatry

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Summary. The developmental perspective as reflected by investigations of childhood and early-onset schizophrenia has become a major research area during recent years and contributed much to the understanding of schizophrenia at all ages.

This paper reviews clinical features, neurobiological and neuropsychological findings in childhood and adolescent onset schizophrenia including some results of studies of the author on age at onset, premorbid symptoms, treatment and course.

Childhood-onset schizophrenia is a rare disorder with a prevalence of one child in 10,000 before the age of 12 and a remarkable increase around puberty and early adolescence. Developmental events and precursors of schizophrenia cover a wide range of dysfunctions and disturbances including elevated rates of soft neurological signs and birth complications, slow habituation and high baseline autonomic activity, high rate of developmental disorders of speech and/or language and overall and specific cognitive deficits. Brain morphological studies and intelligence testing as well as investigations of the course provide evidence of deterioration. Therefore, early-onset schizophrenia can be understood as a progressive-deteriorating developmental disorder.

Keywords: Early-onset schizophrenia, deteriorating developmental disorder, review.

Introduction

Schizophrenic disorders in childhood are rare conditions within the spectrum of psychoses. There are no reliable epidemiological data that could be looked upon as representative. This may be due to the fact that different investigators have used different definitions and several heterogeneous disorders have been subsumed under the heading of "psychoses in childhood". Nevertheless, it is assumed that only 0.1 to 1% of all schizophrenic psychoses manifest themselves before the age of 10 years. In the general population, approxi-

mately one child in 10,000 will develop a schizophrenic disorder (Remschmidt et al., 1994). There are few epidemiological studies which are able to confront questions of frequency, age and sex distribution, treatment and course of child and adolescent schizophrenia. Werry (1992) states that the results of studies carried out before 1975 are questionnable, because at the time no internationally accepted classification schemes were available. According to several authors, however, the following statements can be forwarded: The prevalence rate of childhood-onset schizophrenia (manifestation before 12 years of age) is less than one child in 10,000 children between 2 and 12 years of age (Burd and Kerbeshian, 1987). It is estimated that childhood-onset schizophrenia is approximately 50 times less frequent than adult-onset schizophrenia. It is also less frequent than early infantile autism. There is no comorbid association between autism and schizophrenia, either in childhood or in adults. The two conditions are not more commonly observed together than would be expected by chance (Volkmar and Cohen, 1991). Our own studies show that up to the age of 12 years, all psychotic states are rare conditions, but after the 13th year of life, there is a remarkable increase of schizophrenia (Remschmidt, 1988; Remschmidt et al., 1994). The disorder can be diagnosed according by the same criteria as used for adults (Asarnow et al., 1994) according to the current classification systems ICD-10 and DSM-IV.

During recent years, much attention was paid to schizophrenic disorders in childhood. The reason for that might be the hope that an early manifestation of the disorder could give us more insight in the etiological background, paying special attention to the fact that premorbid impairments of schizophrenic patients have been described which support the developmental perspective.

The purpose of this paper is threefold:

(1) to give a general review of our current knowledge on early-onset (childhood- and adolescent-onset) schizophrenia
(2) to demonstrate that early-onset schizophrenia has a developmental background
(3) to demonstrate that the developmental perspective is not sufficient to explain the progressive-deteriorating course of the disorder.

Clinical features

Age at onset and sex differences

All studies that have looked at age at onset agree that schizophrenic disorders are rare before the age of 12 and show a remarkable increase between 13 and 17 years.

In child and adolescent onset schizophrenia, there is a nearly equal sex ratio (Werry et al., 1994; Galdos et al., 1993) and no difference with regard to age at onset between boys and girls. This is in contrast to observations in adult schizophrenia which demonstrate that females have a somewhat later onset which is explained by the assumption that estrogens can delay the onset of schizophrenia in women by raising the threshold of vulnerability (Haefner et al., 1998).

Symptomatology

Schizophrenic disorders in children and adolescents are nowadays diagnosed according to the criteria of ICD-10 and DSM-IV (WHO, 1992; APA, 1994) which are similar. There is, however, an important difference in the duration of the key symptomatology. Whereas a DSM-IV diagnosis of schizophrenia requires a duration of schizophrenic symptomatology for at least 6 months, in terms of the diagnostic guidelines of ICD-10, the presence of a defined symptomatology during a period of one month or more is sufficient.

In addition, the concept of positive and negative symptoms can be applied to schizophrenia in childhood and adolescence (Bettes and Walker, 1987; Remschmidt et al., 1991). Bettes and Walker (1987) found in a large sample of 1,086 children with psychotic diagnoses, aged 5 to 18, that age had a strong effect on the manifestation of positive and negative symptoms. Positive symptoms increased linearly with age, whereas negative symptoms were most frequent on early childhood and late adolescence. This was true both for the total sample of children and a subsample with a psychotic diagnosis. A further finding was a correlation between symptomatology and IQ in the sense that high-IQ children showed more positive and less negative symptoms than low-IQ children. Remschmidt et al. (1991) administered the concept of positive and negative symptoms to a sample of 113 adolescent schizophrenic patients whose last clinical episode could be analyzed in terms of symptomatology and symptom shift from the beginning of inpatient treatment to the end. A differentiation into three types of schizophrenia according to positive symptoms (type I), negative symptoms (type II), and a mixture of both (mixed type) was possible according to the concept forwarded by Andreasen and Olsen (1982). According to a weighted symptom score, the symptomatology of each patient could be positioned on a continuous scale reaching from the extreme pole of negativity (-1) to the extreme pole of positivity ($+1$). The patients were classified at the beginning and the end of the inpatient episode with respect to the severity of the symptoms. A comparison of positive and negative symptomatology revealed a reduction in the number of symptoms with time, but also a clear symptom shift in the direction of negativity within the course of inpatient treatment. This may be, because negative symptoms at the beginning of the episode could be hidden by positive symptoms and probably became evident after the disappearance of the positive symptoms as a result of neuroleptic therapy. Another interpretation, however, is that a high proportion of patients became chronic. An argument supporting the latter interpretation is the fact that a higher proportion (40%) of only type I-schizophrenia patients reached a stage of remission. Furthermore, this study could demonstrate a symptom shift during impatient treatment from type I to type II and type III, but not in the opposite direction. This observation could be interpreted as a sign of deterioration along the line of our argument that schizophrenia can be looked upon as a progressive disorder.

Premorbid development

Several investigators have identified multiple disturbances during premorbid development in children and adolescents with schizophrenia. These can be

subdivided into developmental events and precursors in different areas and *premorbid symptoms of schizophrenia.*

Developmental events and precursors cover a wide range of dysfunctions and disturbances and can be detected already early in life, some of them with a tendency of progression. The most frequently described developmental precursors are listed up in table 1. As the table demonstrates, they reach from soft neurological signs to *overall* cognitive impairments and *specific* cognitive deficits in special areas.

Among the different areas of dysfunction described in table 1, speech and language dysfunction and transient symptoms of pervasive developmental disorders (Jacobsen and Rapoport, 1988) seem to be most important. As far as the former are concerned, they have been found as a substantial feature in several studies. In the NIMH childhood-onset schizophrenia sample, 60% of the children met the criteria for previous developmental disorder of speech and/or language and 34% had transient symptoms of pervasive developmental disorders during the premorbid period (Alaghband-Rad, 1995; Jacobsen and Rapoport, 1988). The last observation is insofar interesting with regard to the diagnostic category of multiplex developmental disorder (MDD) (Towbin et al., 1993) as some of these cases develop schizophrenia later on (van der Gaag, 1993).

Premorbid symptoms of schizophrenia as a rule do not emerge suddenly when the onset of the disorder becomes apparent and needs treatment, they can be found months and even years before. This was demonstrated in a study of 61 children and adolescents with schizophrenia who had been studied in detail during their inpatient treatment (Remschmidt et al., 1994). In order to get information about positive and negative symptoms and other precursors of schizophrenia, the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) was administered. IRAOS is a semi-structured interview that allows to get information about schizophrenic symptoms before the first manifestation of the disorder. The instrument was developed by Haefner and his group (Haefner et al., 1990) and modified to investigate children and adolescents and their parents by the authors. The inter-rater reliability of IRAOS was found to be satisfactory, with Kappa-values between .62 and 1.00 (Haefner et al., 1992). It could be demonstrated that positive and negative symptoms of schizophrenia could be identified even years before the index admission in patients with first manifestation of the schizophrenic disorder beyond the age of 14 as well as in those with age at onset prior to the age of 14. While many patients showed both negative and positive symptoms before the index admission, both categories of symptoms became more frequent and converged at the time of the index admission.

Risk factors and protective factors

Many of the developmental precursors have been looked upon as risk factors for the manifestation of a schizophrenic disorder. However, there is no clear evidence that is really the case. At least, the presence of developmental precursors alone cannot explain the manifestation of a schizophrenic

disorder. Additional processes have to be postulated which contribute to the manifestation of the disorder and which explain why schizophrenia is very rare before puberty and reaches a peak of manifestation around puberty, in spite of the fact that most of the developmental precursors can be identified much earlier. Insofar, *neurobiological* and *psychological* changes during puberty and adolescence may be key issues for an answer to this question. As far as neurobiological factors around puberty and adolescence are concerned that might be important for schizophrenia, the following findings have been discussed (Keshavan and Hogarty, 1999): (1) Myelination of the association cortex and the limbic cortex including hippocampus takes place during adolescence. This is looked upon as a risk factor as neocortical association circuits and limbic circuits may not come into adequate function until late adolescence. (2) Maturation of the prefrontal cortex (PFC) takes place during adolescence and PFC is responsible for executive functions within the frontotemporal network. (3) The role of gonadal hormones seems to be different: Estrogen increases the frequency of synapses in the rat hippocampus (Desmond and Levy, 1997; Woolley et al., 1996), androgens increase the synaptic elimination in the rat (Jordan et al., 1995). (4) A decline of cerebral plasticity can be observed during adolescence. (5) Finally, changes in the dopaminergic innervation of the primate PFC during adolescence were observed as well as abnormalities in periadolescent synaptic pruning (Feinberg, 1982/1983).

These findings have been used to explain the delayed onset of schizophrenia and especially the timing of onset of the clinical manifestation as determined "by late brain maturation processes and peripubertal neuroendocrine changes as well as inadequate socialization and its reciprocal stress" (Keshavan and Hogarty, 1999, p. 538).

With regard to *psychological changes* during puberty and adolescence, the following statements can be made: (1) Advance in pubertal status is related to improved mood and enhanced body images in boys, but in "decreased feelings of attractiveness for girls" (Offer and Boxer, 1991). (2) Pubertal change seems to be more stressful when the adolescent is regarded as different from his peers (Simmons et al., 1983). This could apply also to children at risk for schizophrenia. (3) Visible pubertal changes noticed by others such as height, weight and breast development are more likely to influence the psychological and psychopathological status than "non-public" changes (Petersen, 1988). (4) Pubertal hormonal changes stimulate sexual interests and aggression, but psychological and psychosocial factors are the mediators of sexual behaviour. (5) Perception of body weight during puberty and early adolescence is more important for girls than for boys (Remschmidt, 1994).

In spite of the fact that these neurobiological and psychological changes occur during puberty and early adolescence, it is not clear how they may be related to the manifestation of schizophrenia around puberty.

Less is known about protective factors. These can be subdivided in personal protectors covering coping strategies, self-efficacy and favourable personality traits and environmental protectors including family problem-solving and supportive psychosocial interventions. Also, an antipsychotic medication

can be looked upon as a protective measure with regard to the course of the disorder (Goldstein, 1987, 1995).

Treatment, course and outcome

Four different aspects in the therapy of schizophrenic psychoses require integration (Remschmidt and Martin, 1992): (1) Pharmacological treatment of acute psychotic states and prevention of relapses; (2) psychotherapeutic measures; (3) family-oriented measures; (4) specific measures of rehabilitation. This review, however, touches only the first point. For this review, we identified only three controlled trials of antipsychotic medication in child and adolescent schizophrenia; the first study by Pool et al. (1976) compared Loxitane and Haloperidol with placebo in 75 schizophrenic adolescents (aged 13 to 18) and found both medications superior to placebo. In a study by Spencer et al. (1992) in 16 children and adolescents with schizophrenia (aged 5.5 to 11.7), Haloperidol was found to be superior as compared with placebo. In the only controlled study with an atypic neuroleptic (Clozapine) carried out by Kumra et al. (1996) in 21 patients with schizophrenia (aged 6 to 18), Clozapine was found superior as compared to placebo. However, high rates of neutropenia and seizures were observed in the Clozapine group.

There are more than ten reports on the use of Clozapine in children and adolescents with schizophrenia, two open trials with olanzapine (Mandoki, 1997; Kumra et al., 1998) and only one open trial in patients with schizophrenia (aged 11 to 18) with Risperidone (Armenteros et al., 1997). In summary, all these studies (for review see Toren et al.) demonstrate that atypical neuroleptics are also effective in childhood and adolescent schizophrenia, Clozapine being the most effective agent, however, with unfavourable effects such as neutropenia and epileptic seizures, hypersalivation and weight gain. The latter applies also to Olanzapine.

With regard to *course and outcome,* we found 18 follow-up studies in the literature, including our own. The results of these studies can be summarized as follows: (1) Schizophrenic disorders with manifestation before the 14th year of age have a poor prognosis, the disorder continues to adolescence and can be diagnosed by the same criteria as used for adults (Asarnow et al., 1994); (2) patients with acute manifestation of the disorder and with productive schizophrenic syndromes such as hallucinations and delusions (positive symptoms) have a better prognosis than those with slow manifestation, insidious course and with continuous impairment of cognitive functions and/or depressive states (Remschmidt et al., 1991); (3) premorbid personality is of great importance. Patients who had been described in the premorbid phase as socially active, intelligent and well-integrated children and adolescents have a better prognosis than those who had been cognitively impaired, shy, introverted and withdrawn before the manifestation of their schizophrenic disorder (Martin, 1991; Werry et al., 1991, 1994); (4) finally, the prognosis is also better in patients without any family load of schizophrenia, good cooperation of the family and rapid improvement during inpatient treatment (Martin, 1991; Remschmidt et al., 1991).

Neurobiological findings

Brain morphology

Compared with studies carried out in adult patients with schizophrenia, the following results could be obtained also in childhood schizophrenia (Jacobsen and Rapoport, 1998; Badura et al., 2001): Decreased total cerebral volume, decreased grey matter volume, increased ventricular volume and decreased midsagittal thalamic area. In addition, the midsagittal area of the corpus callosum was found to be significantly increased, probably due to a compensatory process to the reduction of grey matter volume. This can be concluded from the observation that the reduction of total cerebral volume in childhood-onset schizophrenia seems to be caused by a reduction of grey matter volume (Giedd et al., 1996) which was also found in recent post-mortem studies in adults (Selemon et al., 1995). The clinical relevance of these observations as well as their explanatory power for the thesis that schizophrenia can be looked upon as a *progressive* developmental disorder can be based on two important further results of the NIMH early-onset schizophrenia study: (1) There was a strong correlation between negative symptoms in the sample and total cerebral volume in the sense that lower total cerebral volume was associated with higher scores of negative symptoms (Alaghband-Rad et al., 1997); (2) longitudinal brain imaging in the sample (2-year re-scan of 16 patients compared with 24 matched controls) demonstrated that ventricular volume was increasing in the schizophrenic subjects to a much larger extent than in the normal controls (Rapoport et al., 1997). This result is a strong argument for a progressive process, developmental or non-developmental. It is not clear in how far these results are correlated to prenatal migrational disturbances and other pathological findings that have been described in post mortem studies of adult schizophrenic patients (Jakob and Beckmann, 1986, 1994; Bogerts, 1993). In a recent CAT scan study comparing six patients with very early-onset schizophrenia (prior to the age of 12) with 5 patients with onset of the disorder between 12 and 14, Badura et al. (2001) demonstrated a significant enlargement of the inner liquor spaces only in the first group. In addition, they found a correlation between the enlargement of the inner liquor spaces and the duration of the illness.

Biochemical studies

The few biochemical studies carried out so far in children and adolescents with schizophrenia have mainly been concentrated on the neurotransmitter systems during pharmacological treatment. Not much is known about the development of these transmitter systems in humans. There are, however, interesting results from animal research. From animal studies, two systems seem to be important within a developmental perspective of schizophrenia: the glutamatergic system and the dopaminergic system.

Glutamate is the most important transmitter for the pyramidal cells and is much involved in brain development. The glutamatergic system undergoes remarkable developmental changes in rats during adolescence. Adolescent

rats become sensitive to glutamate antagonists and remain so until adulthood (Farber et al., 1995). In a clinical context, the causation of psychotic states by the glutamate antagonist phencyclidine is well-known during adolescence and young adulthood. From these observations, it was concluded that a dysfunction of the N-methyl-D-aspartate (NMDA)-receptor might be a key mechanism explaining adolescent onset of schizophrenia (Keshavan and Hogarty, 1999).

In spite of the many changes the dopamine hypothesis of schizophrenia has undergone, there seem to be some new aspects focussed on the relationship between reduced dopamine activity in the prefrontal cortex and stress-sensitive changes in subcortical dopamine activity (Keshavan and Hogarty, 1999). A dysregulation in the dopaminergic system may cause working memory deficits which have been observed in non-human primates after chemical lesioning of the dopamine innervations to the prefrontal cortex (Brozoski et al., 1979). A reduction of dopamine in the prefrontal cortex was observed also in schizophrenic patients by PET studies (Okubo et al., 1997).

From clinical studies, it is evident that also the serotoninergic system and the noradrenergic system play an important role in schizophrenia. This was demonstrated by Schulz et al. (1997) in a study of biogenic amines during clozapine treatment in a group of 40 patients (aged 14 to 22 years) with schizophrenia, half of them treated with clozapine, the other half treated with standard neuroleptic medication. Blood levels of serotonin, 3-methoxy-4-hydroxy-phenylglycol (MHPG), norepinephrine and epinephrine were significantly higher in the clozapine-treated patients than in the conventionally treated patients. During long-term treatment, higher serotonin levels were associated with significantly less negative symptoms of schizophrenia, whereas higher MHPG levels were associated with less depression. The short-term effects of clozapine were assessed in a second and independent sample, comprising 15 schizophrenic inpatients (aged 11 to 20 years). Weekly ratings of psychopathological symptoms using standard rating scales were performed in parallel to blood-sampling for measurements of biogenic amines and serum levels of clozapine. These measures were obtained for six weeks during conventional neuroleptic treatment and for six weeks during the open-label clozapine trial. Serum levels of serotonin and plasma norepinephrine levels were significantly higher during treatment with clozapine than during pre-treatment with typical neuroleptics. A comparison of plasma epinephrine levels in responders ($n = 7$) and non-responders ($n = 8$) to clozapine revealed that the response to clozapine can be predicted by epinephrine levels prior to initiation of treatment with clozapine. In addition, subjects who responded to clozapine showed increased mean plasma concentrations of MHPG and epinephrine during treatment with this drug in comparison to the levels measured during pre-treatment with typical neuroleptic medication. Non-responders to clozapine failed to show this increase.

Electrophysiological studies

Electrophysiological studies in early-onset schizophrenia have mainly concentrated on two areas: skin conductance and event related potentials. As far as

skin conductance is concerned, marked autonomic reactions (Mednick et al., 1974) and slow habituation as well as high baseline autonomic activity (Gordon et al., 1994) have been observed. At the time being, it is unclear if those schizophrenic children who show high baseline autonomic activity are more therapy-resistent to neuroleptic treatment than those who do not show this type of reaction as found in adults (Gaebel, 1993; Straube and Öhman, 1990).

The ERP studies in schizophrenic children concentrated on four components: Contingent negative variation (CNV), processing negativity (Np.), a late positive component (P300) and hemispheric asymmetry in the amplitude of P1/N1 compoment complex. According to a review of Asarnow and Karatekin (2000), CNV differences between normal and schizophrenic children were not consistently found across several studies. Np was found to be smaller in schizophrenic than in normal children. A diminished Np-amplitude was the earliest consistent ERP index of schizophrenic information processing deficit and reduced P300 amplitudes were consistently observed in schizophrenic children on the span of apprehension and the continuous performance test. As far as latency of the P300 component is concerned, the results are contradictory. Finally, the absence of right-lateralized P1/N1 amplitudes in visual ERPs was consistently found in four studies of schizophrenic children on the continuous performance test and in span of apprehension tasks.

All these results support the notion that schizophrenic children reveal limitations in their processing capacity. Longitudinal studies are urgently needed in order to understand the developmental course of these functions.

Neuropsychological findings

Cognitive impairments

Several studies have found cognitive impairments in patients with early-onset schizophrenia. These comprise (see Table 1) overall cognitive impairments reflected by lower IQ as compared to normal children, but also specific cognitive deficits in different areas (distractability, verbal comprehension and perceptual organization) (Asarnow et al., 1987). In addition, significant developmental delays concerning language development, motor development and coordination have been described (Watkins et al., 1988; Hollis, 1995) and also transient symptoms of pervasive developmental disorders (Jacobsen and Rapoport, 1988). While these results can be looked upon as robust and stable, the question arises if there is a cognitive deterioration during the course of the disorder. This could be demonstrated by the NIMH early-onset schizophrenia study group (Jacobsen and Rapoport, 1998).

Neurointegrative deficits

Fish (1975) has already stated that a schizophrenic genotype may be manifested in infants by a neurointegrative defect which she called pandysmaturation (PDM). This idea goes back to Bender (1947) who first emphasized deviations in neurological maturation in childhood schizophre-

Table 1. Developmental events and precursors of schizophrenia

Soft neurological signs (Fish, 1977)
Neurosensory and neuromotor deficits in "high-risk children" (Erlenmeyer-Kimling et al., 1984)
Marked autonomic reactions (Mednick et al., 1974)
Birth complications (Parnas et al., 1982)
Slow habituation and high baseline autonomic activity (Gordon et al., 1994)
Overactivity in preschizophrenic boys (Done et al., 1994)
Withdrawal in preschizophrenic girls (Jones et al., 1994)
Significant developmental delays (language development, motor development and coordination) (Watkins et al., 1988; Hollis, 1995))
Poor premorbid adjustment in scholastic performance, school adaptation and social functioning (Asarnow et al., 1994)
High rate of developmental disorders of speech and/or language (Asarnow et al., 1995; Jacobsen and Rapoport, 1998) and transient symptoms of pervasive developmental disorders (Jacobsen and Rapoport, 1998)
Overall cognitive impairment reflected by lower IQ as compared with normal children (Asarnow et al., 1994; Spencer and Campbell, 1994)
Specific cognitive deficit in three areas: distractability, verbal comprehension and perceptual organization (Asarnow et al., 1987)

nia. PDM was operationally defined by three criteria, forming an index of PDM: (1) Transient retardation of motor and/or visual motor development quotient; (2) abnormal profile of function on a developmental examination with an inconsistent heterogeneous profile pattern, sometimes failing simple tasks and passing more complex ones; and (3) accompanied by a retardation in skeletal growth.

Fish et al. (1992) reviewed the literature with respect to neurointegrative deficits with risk factors for childhood schizophrenia and found that 12 studies replicated a delayed development in infants of schizophrenics and preschizophrenics. The authors further replicated the contribution of PDM as a marker for a schizophrenic genotype in a sample of the Jerusalem Infant Development Study, following earlier results of this study reported by Marcus (1974) who looks upon cerebral dysfunction in offsprings of schizophrenics as a possible genetic factor. In their own replication study, Fish et al. (1992) obtained the following results: First, there was a significant relationship between the likelihood of PDM and parental schizophrenia; second, there was also a significant relationship between PDM, schizophrenia and impairment of the children on cognitive and motor tests at the age of 10; and third, within this schizophrenic group, a significant correlation was found between obstetric complications and motor scores which did not apply to the entire sample. The whole sample also consisted of children from parents with affective and personality disorders. Although these evaluations by Fish et al. were based only on two out of the three criteria for PDM (delayed development and parallel delay in skeletal growth), the results look convincing and support the hypothesis that PDM may be a marker for a schizophrenic genotype. The importance of this result is underlined by the fact that the relationship of PDM in children

and parental schizophrenia did not occur with any parental diagnosis other than schizophrenia.

Attentional dysfunctioning

For many years, attentional dysfunction has also been looked upon as a biological marker of schizophrenia. According to Holzman (1983), there are four lines of evidence for this association: (1) The replicated fact of attentional dysfunction in schizophrenics, both in episode and remission; (2) attentional deficits in unaffected first-degree adult relatives of schizophrenic parents; (3) attentional deficits as precursor symptoms of schizophrenia in high-risk individuals that predate clinical symptoms by many years. This notion results from high-risk studies; and (4) the hypothesis that attention per se might be genetically transmitted (Cornblatt, 1988). With regard to the distinction of Nuechterlein and Dawson (1994) who discriminate between three types of markers (stable vulnerability markers, mediating vulnerability markers, and episode markers), attentional dysfunction is looked upon as a stable vulnerability marker of schizophrenia spectrum disorder (Cornblatt et al., 1999).

These results raise the question of whether attentional dysfunctions are associated with social dysfunctions in schizophrenia and if they can also predict social deficits in unaffected adults with risk for schizophrenia. These questions were investigated in a study by Cornblatt et al. (1992) in a subsample of the New York High-Risk Project. The total subsample comprised 164 subjects, including 39 offsprings at risk for schizophrenia, 39 at risk for major affective disorders, and 86 normal control subjects who were approximately 10 years old when tested on an attentional battery. The main result was that the subjects at risk for schizophrenia were significantly more impaired with respect to social deficits than the two other groups; there was no difference between the subjects at risk for affective disorders and normal controls. Childhood attentional deviance was highly correlated within the schizophrenia risk group, but not in the other groups with regard to the three dimensions of social deficit resulting from a factorial analysis of personality disorder examination items: Social sensitivity, social indifference and social isolation. The authors conclude that (1) attentional deficit at an early age may be an important link to later social dysfunctioning in schizophrenia and probably plays an active role in the schizophrenic process; (2) attentional impairment may be primary to the social deficit; (3) attentional deficit seems to be a stable trait throughout the development in subjects at risk for schizophrenia; and (4) attentional deficit can be detected as soon as children are old enough to be tested reliably, at approximately $2^1/_2$ years of age. Interestingly enough, the relationship between attentional dysfunction and social skills becomes significant at mid-adolescence. This is the time when high-risk subjects for schizophrenia first begin to display their social deficits (Cornblatt et al., 1999).

Communication deficits

Caplan et al. (1992) examined 31 schizophrenic children and a control group matched according to sex and mental age with regard to communication

deficits and formal thought disorders. The study also aimed to discover if the discourse deficits of schizophrenic children were related to clinical measures of formal thought disorder. Speech samples were collected from the children of the Kiddie Formal Thought Disorder Story Game (Caplan et al., 1989) which was videotaped and rated for formal thought disorder and was also transcribed for coding cohesion and reference patterns.

The results show the similarities and differences to the communication deficits known from adult schizophrenia. Several of the children's deficits were similar to those found in schizophrenic adults; they spoke less than normal, mental-aged subjects, and their speech did not have enough links to previous utterances (cohesive ties) and not enough references to people, objects or events that were mentioned in earlier utterances (referential coherence). Schizophrenic children often also break with slow-off speech in order to refer to objects, people or events in their immediate surroundings. Those schizophrenic children with loose associations confused the listener also by the unclear and ambiguous way they referred to their surroundings. With regard to these discourse similarities, the communication deficits of childhood-onset schizophrenia and those of adult schizophrenia can be compared.

In a further study, Caplan and Guthrie (1992) examined the similarities and differences in the communication of 13 schizotypical and 12 schizophrenic children who were matched for age and IQ. The general hypothesis that schizotypical children would show communication deficits intermediate between those of age- and IQ-matched normal and schizophrenic children could partially be confirmed.

Discussion and conclusions

From the review of research in child and adolescent schizophrenia, it is evident that the developmental perspective contributes much to the current understanding of schizophrenic disorders. It is clear that the manifestation of schizophrenia at early age is not a sudden phenomenon, but is the result of many factors that contribute to etiology, age at onset, symptomatology, course and outcome. The many precursor symptoms and events prior to the onset of the disorder raise the question if all these factors can be looked upon as developmental factors. The answer to that question is that this is **not** the case. Obstetric complications, e.g., cannot be understood as a developmental precursor, but as an event that might have great impact on future development. The same applies to other stable traits such as attentional dysfunction or event-related potentials that are quite stable over time and can be looked upon as stable vulnerability markers of schizophrenia spectrum disorders (Nuechterlein and Dawson, 1984). Other influences change over time such as speech and language problems, scholastic performance, intelligence or transient symptoms of pervasive developmental disorders. So the developmental perspective covers two different issues: events at early ages that influence the course of development in a certain way and issues that are the expression of a developmental process which implies changes in the respective functions over time. As far as the latter aspect is concerned, changes over time can occur

in two directions, in the direction of improvement and in the direction of deterioration. Recent research has brought forward results that support the notion of deterioration which can be subsumed in the light of four arguments: (1) In the NIMH study group on early-onset schizophrenia, it could be demonstrated that ventricular volume is increasing more rapidly in children with schizophrenia than in healthy children (Rapoport et al., 1997). (2) The same group demonstrated that there is also a deterioration in intellectual functioning during the course of the disorder (Jacobsen and Rapoport, 1998). (3) The long-term course of childhood-onset schizophrenia is extremely unfavourable and worse than in adolescent-onset and adult-onset schizophrenia (Remschmidt et al., 2000a) and (4) during inpatient treatment episodes of patients with adolescent schizophrenia a shift from positive to negative symptoms could be demonstrated which is also a sign of deterioration and a chronical course of the disorder (Remschmidt et al., 1994).

All theories that try to explain schizophrenia are faced with the fact of a peak of manifestation around puberty. There are indeed arguments and results which can be put forward to explain the delayed onset of schizophrenia in spite of the many developmental events and precursors that can be found at much earlier ages. There are three lines of arguments that can be put forward: (1) It is possible that certain genes that predispose to schizophrenia, could be turned on during puberty and adolescence. To date, there are no empirical results that could support this hypothesis. However, during the last years, several candidate regions (currently seven) have been identified in a replicable manner by linkage studies. These regions are likely to host susceptibility genes for schizophrenia, but none of them has been identified so far (Maier et al., 1999). (2) Neurobiological and/or psychosocial maturation processes could either trigger the disorder or lower the threshold for the manifestation around puberty or early adolescence. (3) In the light of a modified vulnerability-stress model, biological conditions (genetic risks, birth complications, neurosensory and neuromotor deficits) and developmental precursors (overall specific cognitive impairments, delayed speech and/or language development, poor adjustment in school) could accumulate and interact with each other and lead to a manifestation of a schizophrenic breakdown when a certain individually variable threshold is reached. As puberty and early adolescence is a time with high demands, the manifestation of the disorder is likely in those subjects who carry a high risk. In general, however, adolescence is not a time of frequent psychiatric disorders or turmoil as the storm-and-stress model of adolescence proposed (Remschmidt, 1994).

In conclusion, there are now ample results and argument for understanding schizophrenia as a progressive-deteriorating developmental disorder.

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