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# The ESSEN study of childhood-onset schizophrenia: Selected results

**Abstract** *Introduction:* We present the results of a 42 year long-term follow-up of 44 patients (19 males, 25 females) with childhood-onset schizophrenia (COS, age at onset: 7–14 years) who could be traced for a second follow-up examination 27 years after the first follow-up. *Method:* Data from interviews, clinical records, premorbid and social disability assessments were evaluated for statistical analyses. The symptomatology observed during the whole course of illness was re-diagnosed by DSM-IV criteria. *Results:* The paranoid, catatonic, and schizo-affectives subtypes appeared most frequently. There have been no gender differences in age of first psychiatric symptoms (AFS), AFPS, and age of first hospitalization. Kaplan-Meier's survival-analysis carried out for AFPS with sex as the grouping factor revealed that the cumulative prevalence appears to be earlier in females (between 7 and 15 years) than in males (between 10 and 18 years). Of the 44 patients 50 % had a continuing severe course. Patients with onset before 12 years of age were characterized by a chronic/insidious onset, marked pre-morbid abnormalities, and by a poorer remission. Premorbid features of social withdrawal and reluctance indicated a risk for social disability within the later course. *Conclusion:* COS, as a rare but severe variant of schizophrenia, frequently develops from premorbid social maladaptation to an insidious onset but is subsequently followed by a transition to a course and outcome not distinguishable from that of adult-onset schizophrenia.

**Key words** Childhood-onset schizophrenia – adolescent-onset schizophrenia – long-term course – premorbid development – outcome

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## Introduction

Contrary to childhood-onset schizophrenia (COS) there are a large number of course studies of schizophrenic psychoses for adults. In their meta-analysis of 320 course studies, Hegarty and colleagues (22) reported follow-ups between 1 and 40 years, 5.6 years on the average (median: 3.0 years). In most of the analyzed course studies, the observation time was rather short; in 57 % it was shorter than 5 years. Only 5.7 % of the courses had time spans of 20 years and more. The conclusion of this analysis is that true long-term follow-up studies are rare even for schizophrenic psychoses of adult patients. Table 1 shows some long-term follow-up studies of schizophrenia in adults. The number of patients and their different observation-periods are recorded.

Especially rare are follow-up studies of schizophrenic psychoses with early onset, most of them had a relatively short observation time between 1 and 5 years (3, 11, 12, 35, 39, 46, 47). This is due to the extremely low frequency of COS (age ≤ 14 years), the prevalence is about 0.14 : 1000. That it is nearly 50 times lower than in the case of later onset.

Schizophrenic psychoses can be diagnosed reliably in children using the same criteria as for adults (2, 12, 17, 40, 44, 45). The use of comparable criteria across age facilitates analyses of progressive symptomatology from childhood to adulthood. However, there are important differences between early-onset and late-onset schizophrenia: The former may be characterized by poor pre-morbid adjustment, a predominance of insidious versus acute onset, and poor prognosis (3, 11, 12).

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**Table 1** Long-term studies of schizophrenia

| Authors | Observation period | Number of patients | Mean age of patients | |
|---|---|---|---|---|
| M. Bleuler, 1978 | 23 years | 208 | at begin of investigation: | 40 years (16–67) |
| Eggers, 1973 | 15 years | 71 | at onset of illness: | 11 years (7–14) |
| Ciompi, 1980 | 37 years | 289 | at first hospitalization: | 37.3 years |
| Huber et al., 1980 | 22.4 years | 502 | at onset of psychosis: | 27.6 years |
| Tsuang et al., 1979 | 30–40 years | 200 | at hospitalization and begin of investigation: | 29 years (21–37) |
| McGlashan, 1984 | 15 years | 163 | at first hospitalization: | 23 years |
| Harding et al., 1987 | 20 years | 82 | at follow-up: | 61 years |
| Marneros et al., 1992 | 25 years | 148 | at onset of psychosis: | 27.7 years |
| DeSisto et al., 1995 | 35 years | 299 | at hospitalization and begin of investigation: | 42 years |
| Eggers & Bunk, 1997 | 42 years | 44 | at onset of illness: | 11.8 years |
| | | | at onset of psychosis: | 13.0 years |
| | | | at first hospitalization: | 13.4 years |

One problem of assessing psychotic disorders in very young children is to determine whether non-specific behavioral disturbances represent an incipient psychosis or are signs of autism or pervasive developmental disorder (PDD) (7, 44). Furthermore, developmental status affects the expression of the disorder. In contrast to cross-sectional evaluation, in long-term follow-up studies it is possible to overcome these diagnostic problems.

This study presents data from a long-term investigation of COS patients and the first results from a group of patients with adolescent-onset schizophrenia (AdOS). Our report focuses upon the age- and gender distribution at onset, the type of onset, the premorbid development and its relation to global social adaptation.

## Methods

### Subjects

*Two samples of patients were under investigation*

The project started with the first sample consisting of COS patients examined for the first follow-up between 1965 and 1967. At that time the mean follow-up period was 15 years. The results of this first examination were published in 1973 and 1978. In 1994/95 the second follow-up examination was carried out after a mean follow-up period of 41.9 years since the onset of psychotic symptoms (13).

The subjects represent an age selected population of all in-patients admitted to a University Psychiatric Hospital in West Germany between 1925 and 1961: all first admissions at this time were scrutinized for patients with a diagnosis of COS. Of the 57 patients with COS examined at the first follow-up, 44 could be traced after 27 years for the second follow-up examination.

The second sample includes 44 juvenile AdOS patients (25 males, 19 females) of our clinic in Essen, who had been hospitalized for schizophrenic disorders between 1979 and 1988. The mean age of onset was 15 years. Follow-up interviews were carried out between 1996 and 1998. A high proportion of cases were seen personally (38/44), in 6 cases first degree relatives and members of the hospital staff gave detailed information.

### Instruments

The complete medical and psychiatric records, including patients' hospital admissions and data from the first follow-up, were screened by the Instruments for the Retrospective Analysis of Onset of Schizophrenia (IRAOS) (20). At the first and second follow-up examinations we used a detailed and structured interview identical to the guidelines of the Present State Examination (PSE) (48).

The original diagnoses at the onset of psychosis in the COS group was based on the diagnostic criteria of Bleuler and Schneider. The patients were re-diagnosed according to DSM-IV and ICD-10 criteria by four clinical experts (two psychiatrists and two psychologists, Kappa: 0.83 to 0.91). In a final consensus discussion, a diagnostic classification was attempted, which took into account the whole course of illness. The pre-morbid development was assessed with the Modified

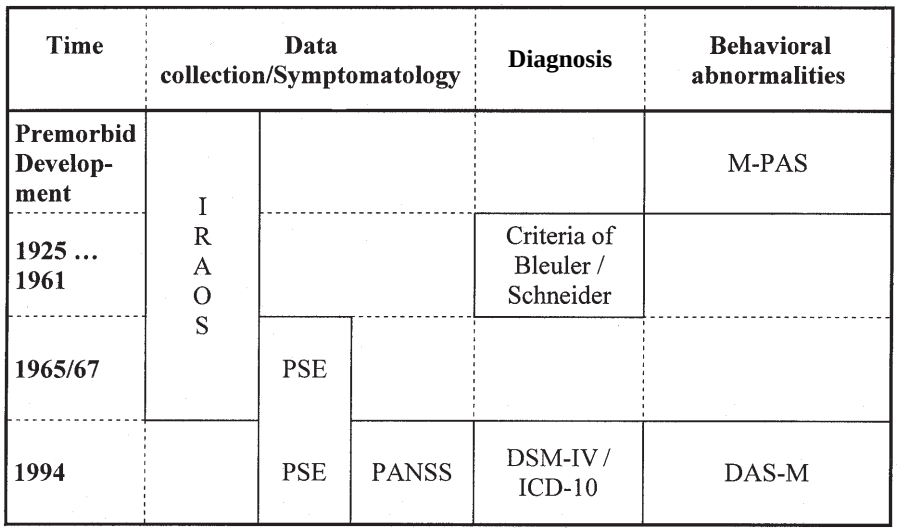


**Fig. 1** Schematic representation of procedures and instruments

Premorbid Adjustment Scale, childhood section (M-PAS) (6, 18). In order to evaluate the psychopathology systematically, we used the Positive and Negative Syndrome Scale (PANSS) by Kay et al. (29) as a symptom checklist.

Global psychosocial functioning at the second follow-up examination was rated with the Disability Assessment Schedule (DAS-M) developed by Jung et al. (28). This scale evaluates the level of social impairment (see Fig. 1 for an overview of the research instruments).

## Results

The 13 patients lost since the first follow-up because of death or unknown change of location did not differ from the remaining 44 patients in gender, age at onset of first psychotic symptoms (AFPS), and the mean frequencies of positive, negative, and global symptoms of the PANSS during the first psychotic episode.

### Distribution of diagnoses

The symptomatology observed during all the consecutive episodes of the disease, i. e., the complete course of illness, was summarized under a single diagnostic category independent of the degree of remission found at the second follow-up. The diagnostic decision for each case was orientated toward the most prominent type of symptoms during the whole observation span (Table 2). The paranoid and catatonic subtype was most frequent. In 10 patients a schizo-affective disorder was diagnosed.

**Table 2** Overall-diagnoses for the whole course of consecutive episodes of schizophrenic/schizo-affective symptoms in COS

| Diagnosis | DSM IV | Diagnosis | % |
|---|---|---|---|
| disorganized | 295.10 | 6 | 13.6 |
| catatonic | 295.20 | 10 | 22.7 |
| paranoid | 295.30 | 15 | 34.1 |
| residual | 295.60 | 2 | 4.5 |
| schizo-affective | 295.70 | 10 | 22.7 |
| undifferentiated | 295.90 | 1 | 2.3 |
| Total | | 44 | 100.0 |

### Age at onset

The mean age at first non-specific psychiatric symptoms, first distinct psychotic symptoms and at first hospital admission of the COS group in comparison with AdOS is shown in Table 3. In both groups, the time-span between age of first non-specific psychiatric symptoms (AFS) and age of first hospitalization (AFH) was nearly identical. But in the COS group, the interval between AFS and AFPS was longer than in the AdOS group, whereas, conversely, the time span between AFPS and AFH was shorter in COS than for the adolescent patients.

**Table 3** Mean age in years of AFS (age of first psychiatric symptoms), AFPS (age at first psychotic symptoms), and AFH (age at first hospital admission) in childhood and adolescent onset schizophrenia

| | AFS | AFPS | AFH |
|---|---|---|---|
| Childhood onset | 11.8 (2.0) | 13.0 (1.7) | 13.4 (1.5) |
| Adolescent onset | 15.0 (1.85) | 15.6 (1.8) | 16.5 (1.9) |

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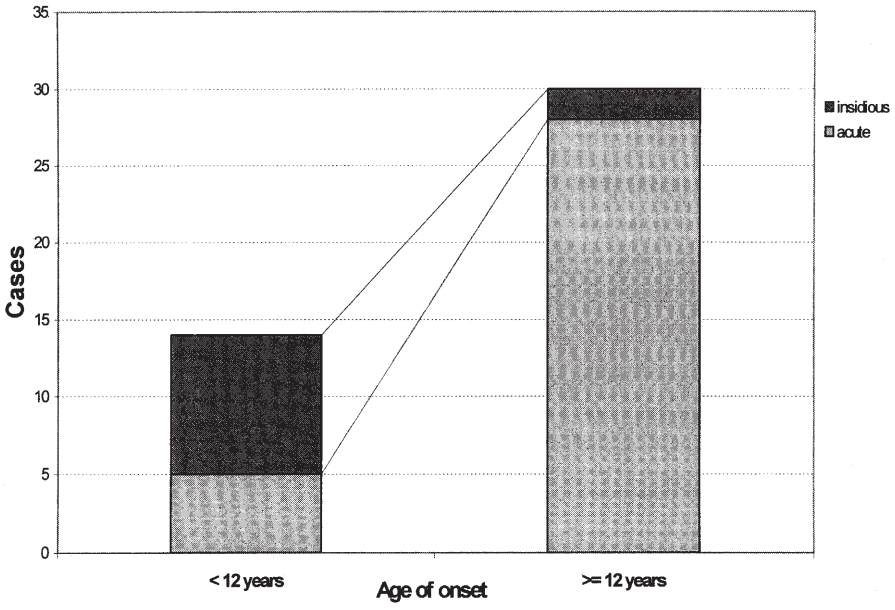


**Fig. 2** Distribution of type of onset in patients with age of onset < 12 years (n = 14) and patients with age of onset > = 12 years (n = 30)

## Gender distribution

A Kaplan-Meier survival analysis with sex as grouping factor revealed that in females the onset of first psychotic symptoms was markedly early (between 7 and 15 years of age) whereas in boys the onset of psychoses covered a time-span between 10 and 18 years of age (13).

## Type of onset and outcome

Onset of psychosis was classified into acute versus chronic-insidious: acute means 4 weeks or less and chronic more than 4 weeks. Eleven patients had an insidious, 33 patients an acute onset. An acute onset was significantly more frequent after age 12, whereas insidious onset predominated before age 12 (Chi-square = 16.9; $p < 0.000$) (Fig. 2).

**Table 4** Distribution type of onset and outcome categories of global social disability (n = 44)

| | Insidious onset | Acute onset |
|---|---|---|
| Complete remission (DAS3 = 0) | 0 (0 %) | 11 (33 %) |
| Partial remission (DAS3 = 1 to 3) | 2 (18 %) | 9 (27 %) |
| No remission (DAS3 = 4 or 5) | 9 (82 %) | 13 (40 %) |

The whole sample was subdivided into three groups using the DAS global psychosocial adaptation score (DAS3) as grouping variable: complete remission (value 0), partial remission (values 1–3), poor remission from psycho-social disabilities (values 4–5). The relation between type of onset and the degree of remission (acute vs. chronic/insidious) is shown in Table 4. In our sample, there was no subject with an insidious onset who was completely remitted from social disability. Eleven patients (25 %) had a very good remission, 11 patients (25 %) were partially remitted, and 22 (50 %) patients were not remitted.

## Relationship between age at onset and outcome

In the first follow-up study, we found that early-onset carried a worse prognosis than later-onset disease (11). This finding was confirmed in the 44 COS patients re-examined at the second follow-up. To exclude any pubertal effects, we divided our study group into those under age of 12 at AFS and those older than 12 years for the comparison of DAS scores. Figure 3 shows the group means for the DAS-M subscales communication deficit/social withdrawal (DAS14), working behavior (DAS26), interest in work and occupation (DAS27), interests/need for information (DAS28), and global social adaptation (DAS3). The ANOVA performed on age-group by DAS-M scores yielded significant differences for all scales; social disability was worse in the group with onset before the age of 12 (n = 14) than in the later onset group (n = 30).

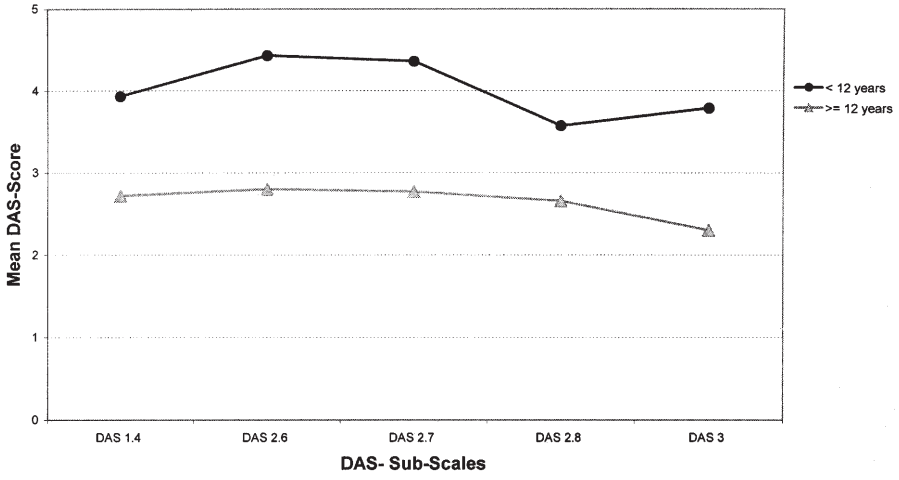


**Fig. 3** Mean DAS scores in patients with age of onset < 12 years (n = 14) and age of onset > = 12 years (n = 30)

Premorbid abnormalities and outcome

Another striking finding was that the children with an age of onset before the age of 12 showed significantly more premorbid abnormalities, rated by the M-PAS global score (Fig. 4).

In order to look for predictive relevance of premorbid developmental abnormalities for the global social disability (DAS3) at second follow-up, a stepwise linear regression analysis was performed. The three M-PAS childhood subscales withdrawal (W), peer relationships (P), and interests (I) were entered as explanatory variables for the dependent criterion variable DAS3. A significant overall correlation was found (multiple R = 0.37, F = 6.6, p = 0.014). Stepwise analysis revealed a significant correlation for the M-PAS subscale W (Beta = 0.37, T = 2.57, p = 0.0138), while the other two subscales did not contribute to the variance of DAS3. Withdrawal during childhood development can be interpreted as a relevant sign of social impairment in the late stages of illness in COS.

## Discussion

In contrast to other studies we could not state a preponderance of male patients in our sample. There was even a slight predominance of female patients, the ratio being 1 : 0.76. These findings are in line with those of Galdos et al. (15, 14), Lewine (31), Matsumoto (34), Jacobsen and Rapoport (26), and Werry (45), but they are in contrast to other authors. How can these differences be explained?

One reason may be the differences in age distribution in the various samples (Table 5). A low age of onset may be associated with a higher proportion of male patients. This could be due to the fact that in very young children autistic-like

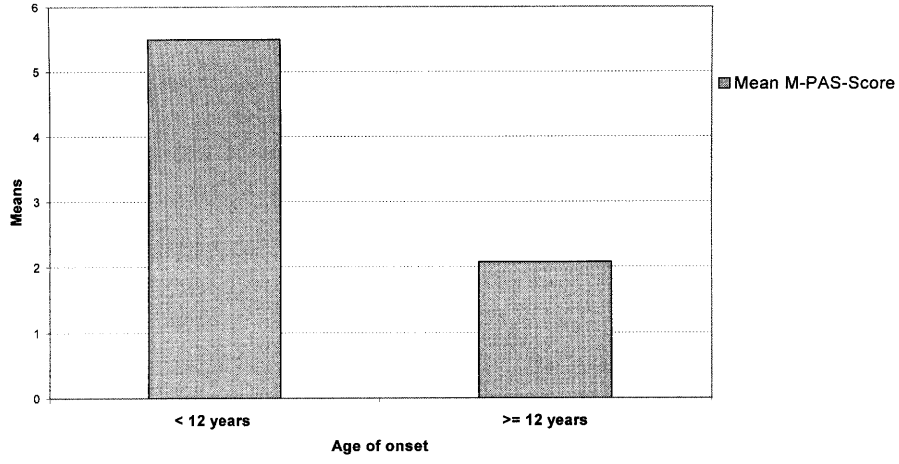


**Fig. 4** Means of total score in M-PAS childhood section grouped by onset of illness before and after 12 years of age

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**Table 5** Selective review of studies: Mean age at onset of Childhood Schizophrenia

| | Onset of non-psychotic symptoms | Onset of psychotic symptoms | First hospitalization |
|---|---|---|---|
| Russel et al. (1989) | 4.6 | 6.9 | 9.5 |
| Green et al. (1992) | 6.4 | 8.6 | 9.6 |
| Maziade et al. (1996) | 7.1 | 14.0 | 15.0 |
| Eggers & Bunk (1997) | 11.8 | 13.0 | 13.4 |

symptoms and/or signs of severe pervasive developmental disorder (PDD) predominate. This is, for example, true for the 18 children with the DSM-III-diagnosis of childhood-onset schizophrenia reported by Watkins and co-workers (44). Similarly Alaghband-Rad and coworkers (1) as well as Russel (39) reported on higher frequencies of autistic symptoms or PDD in their samples. In our sample, however, none of the patients had premorbid features of pervasive developmental disorders or early infantile autism. Table 5 shows the different age groups in the various COS samples.

It is well known that in cases of early infantile autism and/or PDD more males than females are afflicted, rates of the disorder being four to five times higher in males than in females. Thus, indeed, the different age groups could explain the gender differences in the different samples. In this context it is interesting to note that symptoms of PDD have not been reported in the premorbid history of adult onset schizophrenia (10, 27).

No significant gender difference in the morbidity risk of COS was found by the survival analysis, but if one looks at the time at which psychotic symptoms (AFPS) first occurred, one result becomes apparent: all the girls (100 %) were psychotic by the age of 15.0 years, whereas it took until 18 years of age for 100 % of the boys to exhibit true psychotic symptoms. Similar results are reported by Galdos and van Os (14). When assessing gender differences in the onset of psychosis, therefore, the cumulative prevalence over a wide age range (e.g., early school age to late adolescence) ought to be investigated.

For a long time, there was a debate as to whether schizophrenic symptoms analogous to those in adults already appear in childhood. It may now be taken as certain that schizophrenic psychoses can be reliably diagnosed in children using adult criteria according to DSM-III-R, DSM-IV or ICD-10 (2, 4, 11, 12, 17, 40, 44, 45). We agree with Kolvin et al. (30), Reiser (38), Strömgren (42), and Watkins et al. (44) that a schizophrenic psychosis cannot be diagnosed with sufficient certainty before the age of 5 or 6 years, because up to this age the psycho-biological maturation does not yet reach a sufficient level to allow the elaboration of true psychotic symptoms (11, 25). Our results confirm those of Garralda (16) and Watkins et al. (44) that, in general, individual experiences that can be unequivocally diagnosed as delusions and hallucinations do not occur before the age of nine.

In terms of a "whole-course" diagnosis, the paranoid subtype was most frequent in our COS sample. Because of the extremely long observation span of about more than 40 years, the diagnosis is mainly based on the symptomatology observed during adulthood. There is a good agreement with findings from studies of adulthood-onset schizophrenia (19), where the paranoid syndrome was also found to be the most prevalent. The distribution of subtypes in COS is comparable to that of later onset schizophrenia. To classify a life-long course of heterogeneous schizophrenic symptoms into a single diagnostic category may be helpful for clinical communication but the heuristic value for research purposes remains questionable. The disadvantage of this approach is the loss of information about the transition of different symptom profiles emerging across several decades. In this case modern classification schemes like DSM-IV are strongly limited for a clear-cut diagnostic distinction to compare schizophrenic subgroups of varying symptomatology at a distinct point of time. In order to investigate the developing process of the illness and to address research to the relation between schizophrenic core symptoms and the potentially underlying bio-psychological mechanisms a symptom orientated approach might be preferable. In nearly all patients the symptomatology varies markedly during the life-span: episodes of different subtypes were observed within the life-long courses, interfered by episodes of residual symptoms or even by short intervals of relatively good remission (36).

In both samples, the COS and the AdOS group, the time-lag between age of first non-specific psychiatric symptoms (AFS) and age of first hospitalization (AFH) was nearly the same but the time span between AFS and AFPS was longer in COS than in AdOS. This can be explained by two facts: the COS group has been found to contain more insidious-onset patients showing more non-specific symptoms in the early stages of the illness (see Bunk et al. this volume). In addition, because of their less developed cognitive skills, younger children are less capable of expressing clearly their feelings and inner images. Thus, the abnormal behavior of these children could easily be misinterpreted by clinicians and parents as a temporary developmental crisis. This itself renders the diagnosis of their illness difficult. The time-lag between AFPS and AFH was much longer in AdOS than in COS patients. Perhaps the occurrence of psychotic symptoms in adolescents appears to be not so much alarming to the surroundings as it is in younger patients.

At the second follow-up study, 27 years after the first one and an average of 42 years after disease onset, eleven (25 %) of the 44 patients are showing a complete remission (that means DAS3 = 0). This corresponds fairly good to the report of Maziade et al. (35) who found a good outcome in 26 % of their COS patients at an average age of 28 years. Compared to longitudinal studies of adult-onset schizophrenia, this result is close to the findings of Bleuler (5) (208 patients), Ciompi (8)

(289 patients), Huber et al. (24) (758 patients), and Tsuang et al. (43) (186 patients) who found complete recovery in 20 % to 27 % of their cases. In contrast to this, better recovery rates had been published by other authors, e. g., Harding et al. (21) (269 patients), Mason et al. (33) (58 patients), and Shepherd et al. (41) (107 patients). They reported on approximately 50% of complete recovery or significant improvement (no or mild impairment) in their patients. The different results probably originate from varying numbers of patients, follow-up periods, and different criteria for outcome measures.

A further inspection of the individual course characteristics suggests that our schizo-affective patients had no better social adaptation: only 4 of the completely remitted 11 patients fell into this diagnostic category. We assume that poor recovery rates mainly depend on the proportion of time covered by psychotic episodes relative to the whole observation span than on the type of diagnosis.

Premorbid childhood social withdrawal incorporates a risk for marked social disabilities in late adulthood. This meanwhile well-known fact was reported by Hollis (23) and Alaghband-Rad et al. (1) for COS. Marked social withdrawal was found in about 65 % of COS patients. This might be an early sign of possibly bio-psychological developmental abnormalities causing deficit symptoms which accompany the individual for the whole life-span.

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