Pathophysiology of early onset schizophrenia

MARINOS KYRIAKOPOULOS & SOPHIA FRANGOU

Section of Neurobiology of Psychosis, Institute of Psychiatry, King’s College, London, UK

Abstract
Early onset schizophrenia (with onset before adulthood) represents a rarer and possibly more severe form of the disorder which has received particular attention in the last two decades. Current evidence strongly suggest continuity with adult onset schizophrenia, with phenomenological, cognitive, genetic and neuroimaging data pointing towards similar neurobiological correlates and clinical deficits but worse long term outcome. Future research in early onset cases is likely to increase further our insight into the neurodevelopmental origins of schizophrenia and the complex gene-environment interactions affecting its emergence.

Introduction
Schizophrenia is a complex and debilitating brain disorder which commonly presents in early adulthood (Hafner et al., 1993). The current prevailing explanatory theory is that the disorder is neurodevelopmental in origin, with the interaction between genetic factors and environment marking the beginning of brain pathophysiological processes long before the overt manifestation of clinical symptoms. Several lines of research are highly suggestive of a severe form of the disorder with possibly poorer prognosis and more neurodevelopmental insults presenting earlier in life. Within this framework, child and adolescent onset schizophrenia have received particular attention the last two decades as they provide a unique opportunity to explore the aberrant neurodevelopmental origins of the disorder. In this paper, we summarize the current knowledge on the clinical characteristics of the early forms of schizophrenia and discuss the findings from genetic and neuroimaging studies. The term early onset schizophrenia (EOS) is used to describe all cases manifesting before 18 years of age.

Epidemiology
Approximately 4% of all cases of schizophrenia experience the onset of the disorder before the age of 18 (Cannon et al., 1999). The incidence of EOS before puberty is unclear but very small and increases significantly in adolescence (Hafner & Nowotny, 1995; Remschmidt et al., 1994). Thomsen (1996), in a study of 312 Danish children and adolescents admitted to hospital with the diagnosis of schizophrenia between 1970 and 1993, identified only four under the age of 13 and 28 under the age of 15 with the disorder. The hypothesis that puberty might play a role in the onset of EOS has been explored and debated (DeLisi, 1993; Galdos et al., 1993; Galdos et al., 1994; Hollis, 1995; Lewine, 1994). It was more recently also tested by Frazier and colleagues (1997) who found that onset of EOS in children was not correlated with pubertal development. Male sex seems to be more common in these cases with earlier onset but the differences attenuate as age increases (Bettes & Walker, 1987; Green et al., 1992; Kolvin et al., 1971; McClellan & McCurry, 1998; McClellan et al., 1999). However, there have also been studies supporting an equal sex ratio even in younger children (Galdos et al., 1993; Werry et al., 1994).

Clinical features of EOS
Phenomenology
EOS is generally associated with a more insidious onset in comparison to adult schizophrenia, with the younger children being more affected (Asarnow & Ben-Meir, 1988; Kolvin et al., 1971; McClellan & McCurry, 1998; Werry et al., 1991). Studies on phenomenology using structured or semi-structured diagnostic interviews for EOS (Cantor et al., 1982; Fields et al., 1994; Gordon et al., 1994; Green et al., 1992; McClellan & McCurry, 1999; Russell et al., 1989; Russell, 1994; Volkmar et al., 1988)
have consistently reported auditory hallucinations and negative symptoms including flattened or inappropriate affect in this group of patients. Delusions are also a very prominent symptom but are usually less well formed. Catatonic symptoms and bizarre behaviour seem to be less frequent and the identification of formal thought disorder depends more on the sample and definition used (Caplan et al., 2000). It is very important to differentiate between psychotic formal thought disorder and developmental language abnormalities in this group of patients. Overall, symptomatology depends on the age, developmental stage and cognitive abilities of the affected young person (Betts & Walker, 1987; Volkmar et al., 1988). However, despite this, diagnostic stability remains remarkably high (Hollis, 2000; Hollis, 2003; Remschmidt et al., 2006).

Developmental aspects

Language development. Speech and language deficits are of the most commonly observed developmental abnormalities in EOS (Asarnow, 1999; Kolvin et al., 1971; Nicolson et al., 2000; Watkins et al., 1988), probably more frequently than in adult onset cases (Jones et al., 1994; Walker et al., 1994). Alaghband-Rad and colleagues (1995) in a sample of children with EOS, reported 9 out of 21 cases having experienced delay in language development, 10 out of 23 definite articulation disorders, 2 out of 23 probable articulation disorders and 2 out of 23 stuttering. Thirty-three per cent of their sample had DSM-IIIR receptive, expressive or mixed expressive/receptive language disorders. Hollis (1995) in a case-control study of 61 children (range 7 to 17 years) also reported increased speech and language deficits in EOS with child onset cases more significantly affected. In our study (Vourdas et al., 2003), premorbid functioning in EOS was assessed and compared with adult onset cases, as part of the Maudsley early onset schizophrenia project. EOS cases had more speech and language abnormalities compared to healthy controls with male gender being associated with increased vulnerability and the deficits being more prevalent and significant the earlier the age at onset of the disorder.

Psychomotor development. Motor milestones have also been reported to be delayed in adult schizophrenia (Cannon et al., 2002; Isohanni et al., 2001; Jones et al., 1994; Walker et al., 1994). EOS studies also support motor development abnormalities but these seem to be less prominent in comparison to early speech and language problems. In a study by Kolvin et al. (1971), deficits in motor development accounted for 3% of the developmental delays. In a sample of children with onset of schizophrenia before the age of 10 years, Watkins and colleagues (1988) reported a much higher (72%) prevalence of abnormalities in motor development as well as autistic symptoms (39%). In the Alaghband-Rad et al. (1995) Childhood Onset Schizophrenia NIMH study, 6 out of 23 cases had motor coordination disorder at the point of assessment and 2 out of 23 reported history of motor coordination disorder. All these cases had significantly delayed motor milestones. However, only 4 out of 23 cases in the whole sample had motor delays with regards to walking and all children were able to walk by the age of 18 months. Hollis (1995) reported 31% of his sample to have premorbid motor abnormalities including restlessness, stereotyped movements, coordination problems and delayed motor milestones. Nicholson and colleagues (2000) updating on the findings from NIMH study, reported a higher percentage of 57.1% of their sample having motor abnormalities. More males than females had premorbid motor problems similar to those reported by Hollis (1995). In addition, some of their subjects showed autistic features prior to the diagnosis of schizophrenia. In the Maudsley early onset schizophrenia study (Vourdas et al., 2003) there was additional evidence of gross motor deficits, as 3% of the EOS cases could not walk unsupported by the age of 2 years.

Social adjustment. Premorbid deficits in social adjustment and communication have been a very consistent finding in EOS, in keeping with adult onset schizophrenia literature (Amminger et al., 1999; Cannon et al., 1997; Crow et al., 1995; Done et al., 1994; Jones et al., 1994; Malmberg et al., 1998, Norman et al., 2005). Kolvin and colleagues (1971) reported the vast majority of their sample (87%) to be odd before experiencing the onset of schizophrenia while more than half have also been shy, withdrawn, timid and sensitive. Children and adolescents with EOS are significantly more impaired premorbidly in their social adaptation and global functioning in comparison with other psychiatric subjects of the same age (Asarnow and Ben-Meir, 1988; Hollis, 1995; Muratori et al., 2005; Werry et al., 1991). Alaghband-Rad and colleagues (1995) reported about half of their subjects manifesting significant impulsivity and half being relatively withdrawn and asocial. Thirty per cent of their sample met criteria for ADHD and 9% for conduct disorder. More than half of the EOS subjects had failed a grade at school and 65% needed a special educational placement before the onset of their illness. McClellan and colleagues (2003) in their study on early onset psychotic disorders noted a 37% prevalence of schizoid/schizotypal premorbid personality type in those subjects diagnosed with EOS as
opposed to none in those diagnosed with bipolar disorder and 10% in the psychosis NOS group. Thirty-seven per cent manifested behavioural problems and only 18.5% were characterized as having normal premorbid personality. The latter proportion was higher in the other two groups where premorbid behavioural problems were more common. In the Maudsley early onset schizophrenia study, 70.5% of our subjects had premorbidly at least one schizoid/schizotypal trait with social isolation (54%) and odd beliefs or perceptions (41%) being the most prevalent (Vourdas et al., 2003). These patients had more difficulties with social adjustment in childhood in comparison with healthy controls which became even more pronounced during adolescence. Social isolation and poor academic performance were the areas most significantly affected. Developmental abnormalities and male gender were associated with more problems in premorbid social functioning. These problems were also more pronounced in EOS subjects in comparison to adult onset cases (Vourdas et al., 2003). Premorbid school adaptation problems may be a more prominent feature of EOS in comparison to affective psychosis (Schothorst et al., 2006).

Cognitive function

General intellectual ability. Although measuring general intellectual ability might not be completely accurate as the studies exclude those subjects with IQ below 70, most studies report decreased IQ scores in EOS or EOS spectrum patients in comparison to controls (Brickman et al., 2004; Goldberg et al., 1988; Kravariti et al., 2003a, 2003b; Oie & Rund, 1999; Rhinewine et al., 2005; Ueland et al., 2004; White et al., 2006). Gochman and colleagues (2005) evaluated prospectively every 2 years the IQ of the NIMH cohort of children with EOS and showed that after an initial IQ decline starting 2 years before the diagnosis until 1.7 years after, the IQ scores remained stable for over 13 years. This lack of further progression had been previously also suggested by Kravariti and colleagues (2003b) noting that there was no correlation between performance scores and duration of EOS.

Three studies examined the effect of the age of onset in general intellectual ability. Rhinewine and colleagues (2005) compared the childhood onset with the adolescent onset EOS subgroups in terms of premorbid intellectual ability and did not find any differences. White and colleagues (2006) included in their study adolescent onset and adult onset schizophrenia patients whose IQ scores were found to be very similar. Finally, Biswas and colleagues (2006) reported child onset cases to differ significantly in terms of general intellectual ability from both adolescents and adults with schizophrenia. The adolescent and adult subgroups were not significantly different in IQ scores. However, in this study Bonferonni correction for multiple comparisons has not been applied. Studies that compared EOS with other psychotic disorders did not find differences in IQ between the groups (Kumra et al., 2000a; McClellan et al., 2004).

Executive function, memory, attention. A broad range of cognitive deficits have been identified in EOS although not always consistently across studies. Most studies report on generalized neuropsychological dysfunction in EOS with attention, memory and executive function being compromised (Brickman et al., 2004; Kenny et al., 1997; Kumra et al., 2000; Rhinewine et al., 2005). Oie and Rund (1999) also reported on deficits in visual and verbal memory, abstraction-flexibility, spatial organization and motor function but not in visual sustained attention and auditory selective attention. Similarly, the Ueland et al. study (2004) from the same group noted broad dysfunction with executive function and psychomotor speed being most affected but no deficits in sustained attention. In the Maudsley early onset schizophrenia study (Kravariti et al., 2003a, 2003b), EOS patients showed impairment in planning accuracy and visual-motor speed and although they did have reduced initial planning time, like adult onset schizophrenia patients they did not show the typically increased subsequent planning time of adult cases which might be related to increased impulsivity or self-monitoring abnormalities. Memory was also found to be significantly affected in EOS patients, with the general memory scale of the Wechsler Memory Scale - Revised (WMS-R) being substantially lower than the Full Scale IQ score. No deficits in attention that survived Bonferonni correction for multiple comparisons were reported in this study. The inconsistency between the studies with regards to attention deficits might be due to differences in IQ and possibly medication, as the study showing the biggest deficits (Brickman et al., 2004) is the one with unmedicated patients. White and colleagues (2006) who compared early- and adult onset schizophrenia patients both with age matched controls between them found that when accounting for developmental differences only motor performance was worse in adolescent patients in comparison to adult patients. Finally, Biswas and colleagues (2006) identified memory, attention and perceptuomotor skills being more affected in child onset cases in comparison to both adolescents and adults with the last two groups not being significantly different.
Course and outcome

Compared with the adult onset form of schizophrenia it seems that EOS, and in particular the most early onset cases, may be associated with worse prognosis (Jacobsen et al., 1998). Most follow-up studies have found the majority of young persons being chronically ill, with very few having good functioning, and the majority showing poor or very poor outcomes in clinical measures (Fleischhaker et al., 2005; Maziade et al., 1996; McClellan et al., 1993; Remschmidt et al., 2006; Ropcke & Eggers., 2005; Werry et al., 1991). More optimistic outcomes have also been reported (Asarnow et al., 1994b; Pencer et al., 2005; Russell, 1994) with up to around 60% showing significant improvement at follow up. Lay and colleagues (2000) who followed up 65 EOS patients over a period of more than 10 years reported 83% of the patients having at least one further episode needing hospitalization and 74% being under psychiatric treatment. At least moderate educational and occupational impairment was noted in 57% of this sample and serious social disability was found in 66%. Repeated hospitalizations, longer stay and more severe psychopathology predicted worse outcome. Two studies followed up EOS patients over a period of 42 years (Eggers & Bunk, 1997; Remschmidt et al., 2006). In the Eggers and Bunk (1997) study, which examined the outcome of 44 EOS patients, half were found to have continuous symptoms and 25% to be in partial remission. In the most recent study, Remschmidt and colleagues (2006) described the course of 38 patients retrospectively confirmed having the diagnosis according to ICD-10. These cases were identified in a group of 76 patients initially diagnosed with the disorder during childhood. Forty-two years after the initial presentation, the overall prognosis of this cohort was poor, with less than a sixth showing a favourable outcome according to Global Assessment Scale and 60% having a poor outcome. More than 70% did not graduate from school and were unemployed at the time of follow up. The total death rate of the confirmed schizophrenia group was significantly higher from that of the non-schizophrenia group, but death from suicide was not confirmed to be more prevalent among the schizophrenia subjects. Premorbid developmental delay was associated with poor prognosis in agreement with another recent study from the same research group (Fleischhaker et al., 2005). Other studies have identified premorbid function, mode and age of onset, degree of recovery and negative symptoms as predictors of clinical outcome in EOS (Amminger et al., 1997; Eggers & Bunk., 1997; McClellan et al., 1999; Werry & McClellan, 1992). Schmidt and colleagues (1995) compared EOS with adult onset cases and reported unfavourable social outcome in EOS.

Classification of schizophrenia based on age cut-off points has led to the distinction between adolescent- and adult onset cases, for which most studies used the age of 17 – 18, and between child- and adolescent onset cases for which the studies used the age of 11–13. Although there is evidence of earlier onset perhaps being associated with poorer prognosis, these age cut-off points remained arbitrary. A recent study addressing the issue of whether a specific age might be used as cut-off point to delineate worse prognosis (Rabinowitz et al., 2006) used recursive partitioning of an entire population-based cohort from Israel to examine the relationship of the age in first hospitalization with hospitalization outcomes. These included number of days in first admission, percentage of patients with more than one admission, average number of days in hospital and number of admissions per illness year. The authors argued that there is indeed evidence for a cut-off point around the age of 17 and one around the age 12 that mark differential outcome.

Genetics of EOS

Schizophrenia is a highly genetic disorder with heritability of about 80% (Sullivan et al., 2003). The genetic model which is most in keeping with research findings in schizophrenia is the Polygenic/Multifactorial Threshold model (Gottesman & Shields, 1967). This model posits that the probability of developing a disorder is associated with a continuous variable defined as liability. Liability is shared between genes and the environment and the higher it is, the more likely the development of the disorder becomes. Given the high genetic component of schizophrenia, identification of genes contributing to the genetic liability will be crucial in the attempt to understand both gene contributions and gene-environment interactions underlying its emergence. The insights EOS research could offer to this are substantial.

Twin and family studies

Two early landmark studies by Kallmann and Roth (1956) and Kolvin and colleagues (1971) revealed increased familial aggregation for EOS. Kallmann and Roth also reported a higher concordance in earlier age of onset in monozygotic compared to dizygotic twins with schizophrenia, suggestive of a significant role of genetic factors in the earlier presentation of the disorder. Asarnow and colleagues (2001) compared first degree relatives of child onset
schizophrenia cases with relatives of children with ADHD and normal controls and found an increased lifetime risk for schizophrenia and schizotypal personality disorder in the schizophrenia group. Nicolson and colleagues (2003) from the NIMH childhood onset schizophrenia study reported the rates of schizophrenia spectrum disorders in the relatives of the child onset patients being higher than those of the relatives of adult onset cases and control subjects. However, it was mainly an excess of paranoid and schizotypal personality disorders rather than schizophrenia or schizoaffective disorder that seemed to account for this effect. The interviewing clinicians were not blind to patient status but additional blinded scoring of these interviews showed good reliability. Two studies comparing neurocognitive measures of relatives of childhood onset schizophrenia cases with relatives of ADHD probands and controls (Asarnow et al., 2002; Gochman et al., 2004) reported subtle deficits in relatives of the schizophrenia group. Logistic regression models used in the Asarnow et al. (2002) study were also able to discriminate between the groups. Smooth pursuit eye tracking performance, a biological marker for schizophrenia already shown to be impaired in childhood onset cases (Jacobsen et al., 1996b; Kumra et al., 2001), was also used in their relatives, adult onset cases’ relatives and controls to show a worse performance compared to controls in the child onset but not the adult onset group (Sporn et al., 2005).

Family-based association studies

The NIMH group has identified four susceptibility genes in childhood onset schizophrenia while at the same time studied, with negative results, genes (GRIK2/Glu6, Jamain et al., 2002; SLC6A4, Kim et al., 2002; and Klauck et al., 1997; ADA, Lucarelli et al., 2002; GABRB3, Menold et al., 2001; RELN Persico et al., 2001; GRM 8, Serajee et al., 2003; WNT2, Wassink et al., 2001) previously reported to be associated with the diagnosis of autism (Sporn et al., 2005). The susceptibility genes identified were the 13q33.2 gene G72/G30 (Addington et al., 2004), the 2q31.1 gene GAD1 (Addington et al., 2005), the 6p22.3 gene DTNBP1 (Gommick et al., 2005) and the 8p12 gene NRG1 (Addington et al., 2007) all of which have been previously linked with schizophrenia (Harrison & Weinberger, 2005). Among the phenotypic measures for these associations were clinical phenotype (G72/G30), abnormal grey matter loss (GAD1), premorbid endophenotype (DTNBP1) and grey and white matter volumes (NRG1). The identification of susceptibility genes in EOS is very important as it may shed light on the roles of genes in the modification of the developmental trajectories in the disorder (Rapoport et al., 2005).

Cytogenetic abnormalities

Cytogenetic abnormalities were more common in the NIMH childhood onset schizophrenia cohort compared to the estimated rate in the general population. Five out of 47 patients had chromosomal abnormalities including a boy with a t(1;7) reciprocal translocation (Gordon et al., 1994; Yan et al., 2000), a girl with Turner’s syndrome, and two girls and a boy with velocardiofacial syndrome (Nicolson et al., 1999). An additional chromosomal abnormality has been more recently identified by Seal and colleagues (2006) involving a paternal segmental uniparental isodisomy in 5q32-qter. This rate of cytogenetic abnormalities seems to be higher than in adult onset schizophrenia cases and may be associated with earlier onset (Usiskin et al., 1999). Velocardiofacial syndrome, more specifically, is well known to be highly associated with psychosis both in childhood and in adult life (Murphy, 2005).

Other genetic studies

Apolipoprotein E alleles in childhood onset schizophrenia have been investigated by the NIMH group and no differences in the frequency of specific alleles between patients and controls were found (Fernandez et al., 1999). Jacobsen et al. (1998b) in their study of HLA antigens in childhood onset schizophrenia also did not find any association with the disorder.

Neuroimaging of EOS

When considering brain morphological changes in children and adolescents, it is necessary to take the developmental trajectories of brain development into account. Brain grey (GM) and white matter (WM) change markedly in volume during childhood and adolescence; cortical GM follows an ‘inverted U’ course with volumes of different lobes peaking at different times and WM increases in volume with age (Giedd et al., 1996; Lenroot & Giedd, 2006). A ‘back to front’ pattern of cortical GM volume reduction has been part of the maturational process described in normal subjects (Gogtay et al., 2004).

Structural magnetic resonance imaging (MRI) studies in EOS have to an extent given different results in comparison to adult schizophrenia studies, a fact that also partly reflects the differences in developmental stage. Total GM volume reduction and ventricular enlargement are findings from adult studies (Lawrie & Abukmeil, 1998;
Steen et al., 2006; Wright et al., 2000) also replicated in EOS (Frazier et al., 1996; Giedd et al., 1999; Rapoport et al., 1997). Temporal lobe seems less consistently affected; hippocampus has been found not to be affected in some studies (Jacobsen et al., 1996a; Kumra et al., 2000b; Levitt et al., 2001; Matsumoto et al., 2001a) while others support progressive decreases in volume (Giedd et al., 1999; Jacobsen et al., 1998a; Nugent et al., 2006); superior temporal gyrus volume reduction was found in one study (Matsumoto et al., 2001b) while one study reported increased volume (Taylor et al., 2005), three showed no volumetric changes (Jacobsen et al., 1996a; Kumra et al., 2000b; Levitt et al., 2001) and another noted progressive reductions at two-year follow-up (Jacobsen et al., 1998a). Cerebellar (Jacobsen et al., 1997), thalamic (Dasari et al., 1999) and cingulate reductions (Marquardt et al., 2005) have also been reported in EOS. Longitudinal data from the NIMH study also support a back-to-front wave of cortical GM volumetric reduction starting in the parietal lobes, progressing anteriorly (Thompson et al., 2001), together with dorsal-to-ventral frontal GM reductions across the medial hemispheric surfaces clearly separated from cingulate-limbic areas (Vidal et al., 2006) in the EOS subjects. The cortical GM developmental trajectory normalizes in parietal regions and the deficits resemble those seen in adult onset cases with mostly frontal and temporal participation as EOS subjects move into adulthood (Greenstein et al., 2006). Longitudinal date from the Maudsley early onset schizophrenia study show bilateral reductions in EOS subjects in the dorsal and ventral prefrontal cortex, superior parietal cortex, middle and inferior temporal gyrus, thalamus and cerebellum and left-sided reductions in the anterior cingulate, parahippocampal gyrus, cuneus, precuneus and superior temporal gyrus over an average period of four years (Kyriakopoulos et al., in press).

Diffusion tensor imaging has also been used to study WM integrity in EOS. Two studies from the NIMH group (Kumra et al., 2004, 2005) have shown frontal reductions in fractional anisotropy (FA), while the White et al. (2006) study points towards deficits in hippocampal connectivity although these results were not significant after covarying for IQ. Results from Maudsley EOS study show bilateral parietal WM FA reductions in keeping with the hypothesis of early parietal involvement in EOS and also left-sided cerebellar WM FA reductions (S. Frangou, unpublished data; figure 1).

**Conclusions**

EOS research findings point consistently towards continuity between the early- and adult onset schizophrenia, with the former possibly being a more severe variant of the latter. Further investigation of the clinical, cognitive, genetic and imaging characteristics of EOS is likely to contribute significantly to our better understanding of this severe and devastating disorder.

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