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Schizophrenia: A Neurodevelopmental Perspective

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The role of aberrant neurodevelopment in the etiology of schizophrenia is reviewed in light of recent neuropathologic, neurochemical, and neuroimaging evidence of cerebral abnormalities in schizophrenic patients. There may exist some genetic defect in the control of brain development. Clinical epidemiologic surveys highlight the importance of obstetric complications, and prenatal exposure to influenza epidemics in contributing to these abnormalities. It is suggested that such environmental hazards and aberrations in the control of early brain development produce the neuronal phenotype that manifests as schizophrenia with early age of onset of symptoms associated with soft neurologic signs and is more common in young males. ***[Neuropsychopharmacology 9:83–91, 1993]***

KEY WORDS: *Schizophrenia; Neurodevelopment; Etiology; Neuropathology; Epidemiology; Neuroimaging*

The understanding of schizophrenia as primarily a brain disorder, first postulated by Kraepelin, receded in the 1950s and 1960s, but has emerged strongly in the last decade. There is now a plethora of studies that describe neuroanatomic, neurochemical, and neurophysiologic abnormalities in schizophrenic patients (Johnstone et al. 1976; Reynolds 1983; Bogerts et al. 1985; Benes et al. 1986; Jakob and Beckmann 1986; Bruton et al. 1990).

Recent research has suggested that these abnormalities may be developmental rather than degenerative in origin. Here, the role of aberrant neurodevelopment in schizophrenia will be evaluated by considering evidence from neuropathologic, neuroimaging, and neurochemical studies, as well as epidemiologic surveys of obstetric complications and date of birth in schizophrenic patients compared to normal controls.

NEUROPATHOLOGIC EVIDENCE

Although neuropathologic abnormalities were first reported in schizophrenia in the late 1800s and early 1900s (Alzheimer 1897; Wernicke 1900; Klippel and Lhermitte 1909), for the first half of this century the evidence supporting their presence was conflicting. Postmortem research was beset by problems, both clinical and scientific. These included inadequate case definition, sampling errors, contamination by effects of treatment, poor controls, and histologic artifact. Early studies also concentrated on cortical rather than subcortical structures. Recently, with improved methods, closer diagnostic agreement and the systematic collection and examination of brains from untreated schizophrenic patients, some consistent findings have emerged. In three well-conducted studies, schizophrenic brains showed a slight but significant decrease in weight and length (Brown et al. 1986; Pakkenberg 1987; Bruton et al. 1990) compared to normal controls. Bogerts et al. (1985) demonstrated a 20% to 30% decrease in the volume of the medial temporal lobe (amyg-

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dala, hippocampus, and parahippocampal gyrus). This finding fits with evidence of particular enlargement of the temporal horn of the lateral ventricle (Brown et al. 1986).

Falkai and Bogerts (1986), in the first use of quantitative cytology applied to this context, demonstrated decreased cell counts in the hippocampus, and in a further study, also found a reduction in volume of the entorhinal cortex along with decreased numbers of neurons (Falkai et al. 1988). Jeste and Lohr (1989) compared schizophrenic with nonschizophrenic patients and normal controls and found a decrease in hippocampal pyramidal cell density with a loss of hippocampal volume in the schizophrenic patients. Benes et al. (1986) reported decreases in neuronal density in other cortical areas (prefrontal cortex, cingulate cortex, and motor cortex). Since gliosis would indicate neuronal injury or degeneration, its absence in many, although not all, schizophrenic patients together with decreases in neuronal counts points to developmental aberrations (Roberts et al. 1987).

Abnormal cell migration during development has also been implicated, because if this process is disrupted, abnormalities in cell position rather than cell number are found (Nowakowski 1987). Deviations in cerebral cytoarchitecture with abnormal cell positioning have been described in schizophrenic brains (Kovelman and Scheibel 1984; Altschuler et al. 1987); however, a recent study did not replicate these findings (Christison et al. 1989). Conrad et al. (1991) showed hippocampal cell disorganization in the left and right hemispheres of 10 schizophrenic patients. Jakob and Beckmann (1986) reported abnormalities in layer II of the entorhinal cortex with displacement of some of the cells into layer III.

Other neuropathologic evidence, however, mitigates against a solely prenatal explanation for all the lesions found in schizophrenic brains. In earlier work, gliosis was often reported in schizophrenia (Winkelman and Book 1949; Stevens 1982) and more recently, Bruton et al. (1990) found that a surprisingly large number of schizophrenic brains showed focal pathology compared to controls (40%). In patients with focal pathology, fibrillary gliosis was also found affecting the cerebral cortex, the white matter, and periventricular regions. This leads us to conclude that in those patients with focal pathology, either the damage was acquired as a reactive response to cerebral insult or may represent secondary vulnerability to damage due to underlying structural changes (Roberts 1991).

Thus, neuropathologic findings appear to demonstrate multiple lesions in schizophrenic brains, some of which may have a developmental explanation. Just how these lesions arise is yet to be precisely defined. Researchers have postulated abnormalities in fetal cell proliferation and migration (Nowakowski 1987; Murray et al. 1988) due to genetic factors or environmental insult. Interference with the normal process of selective neuronal death during early life leading to axonal disorganization and neuronal misconnections has also been suggested (Benes et al. 1986; Goodman 1989; Lewis et al. 1989).

NEUROIMAGING EVIDENCE

Structural Findings

The evidence of brain abnormalities in schizophrenic patients found by recent neuropathologic research has received support from neuroimaging studies. Pneumoencephalographic investigation (Jacobi and Winkler 1927; Lempke 1935; Huber 1957) were the first to reveal ventricular enlargement in schizophrenic patients which remained static over a 20-year follow-up period (Huber et al. 1985). These nonprogressive changes were related to the clinical defect state of personality disintegration and poor outcome and were thought by these investigators to be congenital in origin.

Computerized Tomography Studies. Computerized tomography (CT) studies substantiated the earlier findings. Johnstone et al. (1976) and others (Nasrallah et al. 1982) demonstrated ventriculomegaly. This is present at the onset of positive symptoms (Schulz et al. 1983; Turner et al. 1986) and in some cases before florid illness emerged (O'Callaghan et al. 1988). These changes have also been shown to be nonprogressive (Illowsky et al. 1988; Vita et al., 1988). The prevalence of ventricular enlargement in schizophrenic patients is unclear and is clouded by the fact that different research groups have used varying cut-off points to distinguish normal from enlarged ventricles (Andreasen et al. 1982); they have also examined different types of patients, either chronically or acutely ill. The specificity of the changes to schizophrenia has been questioned. Harvey et al. (1990) performed a CT scan study of 72 patients compared to 50 community controls. Of the patients, 37 were diagnosed schizophrenic, 15 schizoaffective, 11 bipolar, 5 major depression, and 4 unspecified psychosis. Schizophrenics showed enlarged ventricles but there was no diagnostic specificity for increased ventricular–brain ratio (VBR); the lateral ventricular size of bipolar patients lay between that of schizophrenics and normal controls.

It appears from the above, that there is a subgroup of schizophrenic patients in whom enlarged ventricles have been clearly documented. The task for investigators has been to clearly define this group on epidemiologic, clinical, and neuropsychologic parameters. If CT changes can be correlated with these clinical indices it may help explain the origin of the abnormalities.

CT Studies and Clinical Parameters. Increases in VBR have been associated with evidence of premorbid psychopathology (Weinberger et al. 1980). There is some evidence that structural abnormalities relate to poor premorbid adjustment and many, but not all, studies report a relationship with neuropsychologic impairment (Crow 1985). Johnstone et al. (1989a) demonstrated that cognitive impairment was significantly related to brain area in early onset but not in late onset cases. The former group of patients are far more likely to be male and to have shown personality and cognitive deficits in childhood (Aylward et al. 1984; Foerster et al. 1991). Foerster et al. (1991) point out the similarity between this male predominance and that in neurodevelopmental disorders such as autism and dyslexia.

Comparisons between "familial" and "nonfamilial" schizophrenic patients have been made to determine whether there is an excess of CT abnormalities in those individuals not at high genetic risk. Harvey and Murray (1990) reviewed the evidence. Of 16 singleton studies, 9 were acceptable methodologically. Three studies found no relationship between VBR and family history (Farmer et al. 1987; Williams et al. 1985; Weinberger et al. 1981), whereas others supported ventricular abnormalities as being more common in the population of patients not obviously at high genetic risk (Turner et al. 1986; Owen et al. 1989; Reveley and Chitkara 1985). The issue was confused by the inclusion in some studies of probands whose relatives had affective psychosis rather than only those whose relatives were schizophrenic. Indeed, Owen et al. (1989) in a case control study, reported that schizophrenic probands with an affectively ill relative differed from other schizophrenic probands in having no evidence of ventricular enlargement. Thus it would be premature to draw conclusions on the nature of CT changes in familial or sporadic subgroups based on currently available evidence until further, better controlled studies become available.

Magnetic Resonance Studies. Magnetic resonance imaging (MRI) studies have not only confirmed the CT findings of enlarged ventricles in schizophrenic patients but have also shown smaller volume of brain structures, in particular the temporal lobe and hippocampus (Suddath et al. 1990; Bogerts et al. 1990; Andreasen et al. 1986; Johnstone et al. 1989b). Harvey et al. (1992) reported a generalized decrease in cortical volume in schizophrenics compared with controls, suggesting that the temporal lobe findings are simply one manifestation of a more diffuse process affecting cortical grey matter. Bogerts et al. (1990) also noted that hippocampal volume was significantly smaller in the left hemisphere of male patients. Gur et al. (1991), in an MRI volumetric analysis of brain and cerebrospinal fluid (CSF) in 47 schizophrenic patients and 47 controls, found higher ratios of sulcal CSF to cranial volume in male but not female schizophrenic patients compared to controls. This is in accord with much other evidence of greater structural abnormalities in males than in female schizophrenics (Castle and Murray 1991).

Studies of Discordant Twins. Twin strategies have been particularly useful in trying to disentangle whether neuroimaging abnormalities are genetic or acquired. As monozygotic (MZ) twins are genetically identical, differences between them must be due, at least in part, to environmental factors. A study using the Maudsley twin register showed that ventricular size was strongly genetically determined in a series of healthy MZ twin pairs, and that the correlation in ventricular size was lower in MZ pairs discordant for schizophrenia. Furthermore, the schizophrenic twins had significantly larger ventricles than their nonschizophrenic cotwins (Reveley et al. 1982; Murray et al. 1985b). Interestingly, the nonschizophrenic cotwins had larger ventricles than those of MZ twins from completely normal pairs. This suggests that an environmental factor caused increase in ventricular size in both members of the discordant pair, only the more severely affected twin becoming schizophrenic.

An MRI study of 15 pairs of MZ twins discordant for schizophrenia confirmed increased ventricular size (particularly in the lateral ventricles and the third ventricle) in the affected twins, as well as loss of hippocampal volume on the left and right in affected compared to nonaffected cotwins. No such intrapair differences were found in seven pairs of control twins (Suddath et al. 1990). The findings of these two twin studies add support to acquired rather than genetic factors being of etiological importance, at least in the twin population. Environmental pre- or perinatal factors may of course be more important in schizophrenic twins than schizophrenic singletons because of the greater liability of twins to obstetric complications. To reinforce caution in extending twin findings to the general schizophrenic population, Lewis et al. (1990) reported an intriguing case of identical twins in whom the schizophrenic twin showed no brain abnormalities on MRI but the unaffected twin had extensive right temporal damage of congenital origin.

Functional Findings

The last decade has witnessed great advances in imaging techniques measuring brain function in the living human (positron emission tomography [PET] and single photon emission tomography [SPET]). It is now possible to examine brain metabolism, cerebral blood flow (tightly coupled with brain metabolism), and a variety

of neurotransmitter receptors. Applying these techniques, it may be possible to correlate structural with functional deficits, and assess whether functional abnormalities are the cause or consequence of structural lesions. This is a burgeoning research area that will not be discussed in depth here.

Early PET investigations found decreased frontal cortical glucose metabolism and blood flow (Ingvar and Franzen 1974; Farkas et al. 1984; Buchsbaum et al. 1982). However, the evidence regarding "hypofrontality" in schizophrenic patients remains conflicting because there are many methodologic and technical differences between studies which have not been systematically addressed. Inability to activate the frontal cortex when performing a task-activating condition is said to occur mainly in schizophrenics with predominantly negative symptoms (Garza-Trevino et al. 1990).

Weinberger (1987) asserts that there is evidence of a decrease in cerebral flood flow during mental activity in the left dorsolateral prefrontal cortex in schizophrenics compared to healthy normals (Weinberger et al. 1986; Berman et al. 1986). On the basis of animal studies and the cerebral blood flow pattern in schizophrenics, he implicates this site as a seat of dysfunction in schizophrenia. This is of particular interest as prenatal lesions of the dorsolateral prefrontal cortex in primates are behaviorally silent until the animal reaches the equivalent of human adolescence (Goldman-Rakic 1987). Since these studies, other investigators using PET and SPET have shown deficits particularly in left frontal cortical and temporal blood flow, at rest and during specific neuropsychologic tasks (Liddle et al. 1992; Lewis et al. 1992). Intriguing findings of a left lateralized increase in globus pallidus blood flow and striatal D_2 receptor density in patients compared to controls (Early et al. 1989; Farde et al. 1990; Pilowsky et al. 1993) also suggest disruption of frontostriatolimbic circuits in some patients with schizophrenia. Furthermore, the normal decrement in striatal D_2 receptors with age appears to be lost in schizophrenic patients (Martinot et al. 1990, 1991; Pilowsky et al. 1993), which may be evidence of dysfunctional cerebral maturation. These abnormalities may therefore provide a clue to underlying mechanisms amenable to investigation.

CLINICAL EPIDEMIOLOGY

Genetic factors are well known to operate in schizophrenia, perhaps by some defect in the control of neurodevelopment (Jones and Murray 1991). However, environmental factors are likely also to be of etiological importance. Schizophrenic patients are more likely than healthy controls and other psychiatric patients to have a history of pre- and perinatal hazards and to be born premature. Henceforth the term obstetric complications is taken to refer to deviations from normal pregnancy, delivery, and early neonatal period (McNeil and Kaij 1978; Lewis and Murray 1987). Most recently, Eagles et al. (1990) studied schizophrenic patients using their healthy siblings as controls. They standardized criteria to diagnose schizophrenia and to scrutinize birth records blind to adult outcome, thus overcoming many of the methodologic shortcomings of previous studies. They found a strongly significant excess of obstetric complications in schizophrenics compared to healthy controls (although no single complication was particularly implicated). Such complications appear particularly in the histories of male schizophrenics, are associated with early age of onset, and with increased ventricular size (Lewis et al. 1989; Castle and Murray 1991).

A history of an affected relative and a history of obstetric complications tend to segregate separately, suggesting that some early cerebral insult such as hypoxia may induce phenocopies in those individuals less predisposed genetically (Murray et al. 1988). This argument gains support from the fact that the pyramidal cells in the hippocampus—an area known to be damaged in schizophrenia—are extremely vulnerable to cerebral anoxic insult, such as that which may occur during a difficult pregnancy and delivery.

Perinatal complications may explain the occurrence of schizophrenia in some patients but do not account for all the developmental abnormalities found. Foerster et al. (1990) reported that schizophrenic patients had a lower mean birth weight than controls and Lewis et al. (1987) noted that MZ twins discordant for psychosis already showed greater intrapair differences in weight at birth than normal MZ pairs. McNeil (1993) reported significantly smaller head circumference at birth in preschizophrenic patients than normal controls with disproportionately small head size in relation to shoulder width. Small head size occurred preferentially in sporadic schizophrenics but was not associated with obstetric complications. Of course, fetal abnormalities could, in themselves, contribute to difficult deliveries and obstetric complications.

These findings suggest abnormalities in development that antedate the perinatal period. Furthermore, other indicators of developmental disruption during fetal life such as minor physical anomalies are present in excess in schizophrenic patients compared to normal controls (Green et al. 1989). Again, minor physical anomalies are more common in male schizophrenics, predict a younger age of onset, and are associated with cognitive impairment (Green et al. 1987; Waddington et al. 1990). This is also consistent with the notion that early-onset schizophrenia involves a more compromised central nervous system and may constitute a separate subgroup of patients.

Schizophrenics are born slightly more often in the

late winter and spring. This winter excess is not explained by seasonal variation in obstetric complications (O'Callaghan et al. 1991) but investigators have linked the excess of winter birth to viral infection. Mednick et al. (1988) reported on a Finnish birth cohort in which it was found that those in the second trimester of fetal development during the 1957 type A2 influenza epidemic ("Asian flu") were at elevated risk of subsequently being admitted to a psychiatric hospital with a diagnosis of schizophrenia. These authors postulated that a viral infection could disrupt the process of cell migration from the ventricular zone to the neocortex, which occurs around 16 to 24 weeks of gestation. A much larger study from England has since replicated this finding (O'Callaghan et al. 1991).

The schizophrenogenic effects of influenza do not appear to be confined to the "Asian flu" pandemic. Studies in Denmark (Barr et al. 1990) and England (Sham et al. 1991) over 4 and 2 decades, respectively, have shown a consistent rise in schizophrenic births after influenza epidemics. It is not clear whether the etiological factor is influenza specific, or whether other factors, such as maternal pyrexia, commercial medicines, or other associated stresses could be responsible. However Conrad and Scheibel (1987) claim that neuraminidase-containing viruses such as influenza can interfere with intercellular adhesiveness required for smooth migration of developing hippocampal neurons (Nowakowski 1987). Scheibel et al. (1991) have recently claimed that pregnant mice who they infected with influenza produced offspring with hippocampal cell disarray reminiscent of that which these authors earlier reported in schizophrenia (Kovelman and Scheibel 1984). Cortical abnormalities were widespread in these animals, which is perhaps consistent with neuropathologic findings of increased focal neuropathology in schizophrenic patients (Bruton et al. 1990), but caution is required in extrapolating etiological mechanisms from preliminary animal models.

DEVELOPMENTAL NEUROCHEMISTRY

The neurochemistry of schizophrenia has been substantively reviewed in the literature and will not be discussed in depth. In terms of neurodevelopmental influences, the focus here will be on excitatory neurotransmitters and trophic factors rather than monoaminergic systems. Kerwin and Murray (1992) provide a detailed overview of the area.

The neurotransmitter cholecystokinin (CCK) is highly concentrated in the hippocampus (Roberts et al. 1984) and is reduced in this region in schizophrenic brains (Crow et al. 1982; Roberts et al. 1983; Ferrier et al. 1983; Carruthers et al. 1984), whereas cortical CCK seems unchanged (Perry et al. 1981). The hippocampal reduction in CCK has been associated with negative symptoms (Roberts et al. 1983). Excitatory amino acid levels in the temporal region are also diminished, with a loss of glutamergic terminals (Deakin et al. 1989); in addition, bilateral loss of [^{3}H]kainate binding localized in the CA4/CA3 region and inner layers of the entorhinal cortex has been demonstrated (Kerwin et al. 1990).

The above neurotransmitter systems have been found to play a role as trophic factors in hippocampal development. Glutamate and N-methyl-D-aspartate have been shown to stimulate the formation of tau in axons, cell bodies, and dendrites (Mattson et al. 1988). N-Methyl-D-aspartate receptors are vital to the expression of a variety of experience-dependent synaptic remodeling processes (Harris et al. 1984; Kleinschmidt et al. 1987; Bear et al. 1990), and Mattson et al. (1990) have proposed that fine tuning of glutamate systems is primarily responsible for the maintenance and modulation of neuronal architecture. A deficit of these substances in the hippocampus may result in aberrant cell growth in the hippocampus. Alternatively, it is well established that excitatory amino acid receptors mediate some pathophysiologic consequences of ischemia (Collins 1986) and that psychotomimetic antagonists such as phencyclidine and MK-801 can protect against this (Lyeth et al. 1989). It is therefore possible that these excitatory amino acids play a part in mediating the cerebral damage resulting from pre- or perinatal hypoxia.

The CCK receptors are also important in hippocampal development. The CCK receptor number fluctuates during fetal brain development and in the early postnatal period (Hays et al. 1981). Cells containing CCK are arranged in a laminar fashion that could influence the attraction of ingrowing afferents (Chun et al. 1987). Underexpression of CCK receptors, as is found in schizophrenia, could result in the disturbance of cell migration such as is seen in schizophrenia (Kerwin and Murray 1992).

AN ETIOLOGICAL MODEL

Murray and coworkers (1985a, 1988) have contended that schizophrenia is a heterogenous condition with a number of different causes. The condition that most closely approximates Kraepelin's dementia praecox (i.e., schizophrenia of early onset, more common in males, and associated with neurologic soft signs and cognitive impairment) is likely to be the consequence of aberrant neuronal development during pregnancy and the neonatal period. It is associated with a variety of macro- and microscopic abnormalities including increased ventricular size, cortical (especially temporal) dysplasia, and disordered hippocampal cytoarchitecture. The nonprogressive nature of these changes suggests that they are developmental anomalies which may

be consequent upon inheritance of mutant genes, fetal, or neonatal adversity or a combination of the two. The question of why florid psychotic symptoms do not develop until early adulthood has led researchers to speculate that the neural dysplasia remains quiescent until it is unmasked by brain maturational changes, possibly synaptic pruning or myelination (Murray et al. 1988; Benes 1989; Pilowsky and Murray 1991).

Developmental theories do not account for other types of schizophrenia, for example, late onset, or transient, good prognosis illnesses. These illnesses occur particularly in women and in those with a relative suffering from affective disorder; such individuals may have a disorder that has more in common etiologically with affective disorder. Indeed, Murray and O'Callaghan (1991) suggest that the Kraepelinian distinction between schizophrenic and manic-depressive psychosis should be abandoned in favor of a distinction between psychosis of neurodevelopmental and adult origin.

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