Structural brain imaging abnormalities associated with schizophrenia and partial trisomy of chromosome 5

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SYNOPSIS

Chromosomal abnormalities occurring in association with mental illness provide a unique opportunity to study the interaction of genetic abnormalities and the brain in mental illness. Four individuals from a family in which schizophrenia was found to cosegregate with a partial trisomy of chromosome 5 were studied with computed tomography and magnetic resonance imaging. Temporal lobe atrophy was found in the two trisomic males and in the asymptomatic balanced translocation female. In addition, a large cavum septum pellucidum and a cavum vergae were found in the older trisomic individual. Scans from the normal male were free of abnormalities. These results suggest that molecular studies of the translocation breakpoints in this chromosomal abnormality may be of interest, and encourage further studies of brain structure in other chromosomal abnormalities associated with psychosis.

INTRODUCTION

Cytogenetic anomalies associated with illness have provided valuable insight into the genetics and pathophysiology of disorders such as muscular dystrophy and acute promyelocytic leukemia (Ray *et al.* 1985; Borrow *et al.* 1990; de The *et al.* 1990). Interest in cytogenetic abnormalities occurring in association with mental disorders has increased in parallel with the widespread application of genetic linkage methods to the study of psychiatric disorders (Bassett, 1992). The description of a family in which schizophrenia was found to cosegregate with a partial trisomy of chromosome 5 (5ql 1.2–ql3.3) provided an opportunity to evaluate the possible role of this abnormality in the genesis of schizophrenia (Bassett *et al.* 1988). Characterization of the phenotype of this family is therefore of considerable interest.

The proband and his maternal uncle have an unbalanced translocation of a portion of the long arm of chromosome 5 into the long arm of chromosome 1, in effect, a partial trisomy of

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chromosome 5. The proband's mother has a balanced translocation. Like the proband, she has a rearranged chromosome 1, containing the inserted segment of chromosome 5. However, a corresponding deletion in one of her chromosomes 5 gives her a normal total complement of genetic material. The proband's brother has normal chromosomes. The partially trisomic individuals in the family have an unremarkable schizophrenic illness, smooth pursuit eye movement abnormalities typical of those reported for schizophrenia (Iacono *et al.* 1988) and a cluster of minor physical anomalies (McGillivray *et al.* 1990). The proband's mother and brother do not have psychiatric illnesses, smooth pursuit eye movement abnormalities or physical anomalies. A range of abnormalities of brain structure are reported in cases of schizophrenia, including cortical, subcortical and ventricular abnormalities. The present report concerns the abnormalities of brain structure noted in members of this family.

METHOD

The three family members with chromosomal abnormalities were imaged with computed tomography (CT) and magnetic resonance imaging (MRI), the chromosomally normal brother of the proband was imaged with MRI only. The ages of the individuals scanned were: the proband 22 years, his uncle 53 years, his mother 55 years, and his brother 23 years. None had a significant history of alcohol abuse, hypothyroidism or exposure to corticosteroids. CT scans were performed using a third generation, high resolution scanner (Somatom DR2). Between 16 and 18 slices 8 mm in thickness were obtained approximately parallel to the canthomeatal line. MR scans were performed using a 0.15T Picker International NMR Cryogenic 2000 System. Twelve slices 10 mm in thickness were obtained approximately parallel to the skull base. Three series of scans were obtained for each individual using an inversion recovery sequence ($T_1 = 400$ ms), and two spin echo sequences ($T_E = 40$ ms, 120 ms) with repeat times of 2 s for all scans.

The family was described to a senior neuroradiologist (S.H.), who was asked to evaluate the CT then the MRI scans of each family member for abnormalities, as well as specific patterns of neuroanatomy found to be similar between family members. A second neuroradiologist (D.K. B.L.) performed the same task independently, without knowledge of the diagnosis or cytogenetic status of the individuals. The findings of the first evaluation were confirmed.

RESULTS

The proband was noted to have enlarged fluid filled spaces adjacent to the anterior temporal lobes on CT scan. Temporal lobe atrophy was diagnosed with MRI, the features being enlarged temporal horns, thinned parahippocampal gyri and increased Sylvian fissure prominence (Figs 1 and 2). The proband's uncle displayed similar but more pronounced findings in the temporal lobes. A large cavum septum pellucidum and a cavum vergae were also noted, and were unique to this individual (Fig. 3). The proband's mother displayed the most pronounced temporal lobe atrophy of the three individuals having chromosomal abnormalities. The temporal lobe changes appeared to be bilateral. Further studies with more precise positioning in the scanner would be required to assess asymmetries with accuracy. No additional abnormalities were observed on scans obtained using spin echo sequences.

The proband's brother did not have temporal lobe atrophy or any other abnormality demonstrable on the MRI scan. Of note, when the CT and MRI scans of each individual were initially read separately on a clinical basis, only generalized atrophy in the mother and uncle were noted, as well as the cavae.

DISCUSSION

The brain imaging findings of note in this pedigree are temporal lobe atrophy in each family member with anomalous chromosomes, and a neurodevelopmental anomaly in the older male with a partial trisomy and schizophrenia. The one chromosomally normal individual studied had neither abnormality. Given the small size of this pedigree the results observed could be due to chance. Also, given the known role of genetic factors in controlling aspects of brain morphology even in normal subjects (Weinberger *et al.* 1981; Reveley *et al.* 1982; DeLisi *et al.* 1986) the results could be due to genetic factors other than those contributed by the chromosomal abnormality in this family. However, the findings do suggest several hypotheses which may be worthy of investigation.

The chromosome 5 to chromosome 1 translocation may be associated with anatomical changes in the temporal lobe. Although balanced translocations are usually without phenotypic expression, examples from both human and mouse genetics suggest that translocations can occasionally be associated with behavioural and neurological abnormalities (Fryns *et al.* 1986; Holland & Gosden, 1990; Rutledge *et al.* 1986). Chromosomal translocations can result in the production of abnormal proteins, partially coded for by each of the anomalously joined genes. This is reported to occur in the case of the chromosome 17 to chromosome 15 translocation in acute promyelocytic leukemia (Borrow *et al.* 1990; de The *et al.* 1990). A testable hypothesis is that a gene which is related to temporal lobe structure may be located near one of the translocation breakpoints. The partial trisomy of chromosome 5 may be associated with schizophrenia, although there is insufficient power in the small family studied to make this possibility more than tentative (Bassett, 1989). Genes present in trisomic regions are believed to result in phenotypic abnormalities through gene dosage effects or by dysregulation of the expression of other genes. Characterization of genes within the trisomic region may contribute to an understanding of schizophrenia.

These hypotheses assume that each of the chromosomal abnormalities has a potentially independent role in producing the phenotypic characteristics. Alternatively, an epistatic model (Risch, 1990) predicts that the chromosomal abnormalities interact in some fashion to result in a complex phenotype. For example, the translocation could result in temporal lobe changes which form a substrate for schizophrenia. In the presence of this substrate, an effect due to the partial trisomy of chromosome 5 might lead to the phenotypic expression of the illness.

Relative to other brain regions, pathology of the temporal lobes was most frequently noted to be associated with schizophrenia (Davison & Bagley, 1969). More recent post mortem and neuroimaging studies indicate that structural abnormalities of the temporal lobe occur in both schizophrenia and affective disorder (reviewed in Altschuler *et al.* 1990).

Neurodevelopmental factors may play a role in these abnormalities (Weinberger, 1987; Lewis, 1989). It is of interest that the more severely affected individual in the present study had a developmental abnormality of the septum pellucidum. Although cavum septum pellucidum may be a purely incidental finding at autopsy or on brain imaging, a significant literature reports neuropsychiatric disorders in patients with this abnormality (Lewis & Mezey, 1985). In one autopsy series, cavum septum pellucidum was reported to be more frequent in cases of schizophrenia than in controls (Wildi *et al.* 1967). Midline abnormalities of the brain in general may be more common in cases of schizophrenia and are suggested to be markers for developmental abnormalities (George *et al.* 1989; Uematsu & Kaiya, 1989). Such findings do not, however, imply a developmental basis for all the structural abnormalities reported here. Degenerative changes are an alternative explanation, occurring alone or in association with developmental abnormalities. As an example, trisomy of chromosome 21 results in both developmental and degenerative changes in the brain.

Two conclusions may be drawn from the present findings. First, testable hypotheses concerning the relationship between genetics, brain structure and psychosis can be generated through brain imaging studies of families with chromosomal and psychiatric disorders. Secondly from a methodological standpoint, the approach taken here was purely qualitative, and was based on a search for patterns of anatomy within a pedigree. Application of this paradigm to chromosomally normal families segregating schizophrenia could identify new patterns of brain abnormalities for which quantitative assessments could then be developed and tested.

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FIG. 1.

MRI scans obtained with an inversion recovery sequence from the proband (P), his mother (PM), his maternal uncle (PMU) and his brother (PB). Atrophy of the anterior temporal lobes is apparent in each individual with the exception of the proband's brother.

FIG. 2. Further demonstration of temporal lobe atrophy in individuals P, PM and PMU. Note dilation of the temporal horn, thinning of the parahippocampal gyrus and widening of the Sylvian fissure, most prominent in PM.

FIG. 3.
Large cavum septum pellucidum and cavum vergae seen in the proband's uncle.