No Difference in Basal Ganglia Mineralization Between Schizophrenic and Nonschizophrenic Patients: A Quantitative Computerized Tomographic Study

Manuel F. Casanova, Channavajjala M. Prasad, Ivan Waldman, Barbara Illowsky Karp, Bradley Stein, Danniel R. Weinberger, and Joel B. Kleinman

The role of iron in schizophrenia (SC) has aroused attention because of its modulatory effect on the dopamine receptor and its role as a cofactor for tyrosine hydroxylase. In addition, several postmortem studies suggest that increased mineralization (especially iron) of the basal ganglia is a possible clinicopathological correlate of schizophrenia. In order to quantitate the in vivo *mineral content in the basal ganglia of patients with SC, a protocol was developed to analyze CT scans films with a LOATS computer analysis system. A total of 725 consecutive CT scans (275 SC, 450 nonSC) from a psychiatric population were reviewed. Eighteen scans (2.3%) revealed basal ganglia mineralization of which 7 cases carried a diagnosis of SC and 11 had other psychiatric disorders. All subjects had received neuroleptics, and 8 of the 11 patients in the nonschizophrenic group were demented. Both the SC and nonSC patients exhibited a prevalence (2.5%) of basal ganglia mineralization similar to that found in a postmortem series of the general population.*

Introduction

Several postmortem studies have reported the presence of basal ganglia mineralization in patients with schizophrenia (SC). Josephy (1930) and Stevens (1982a, b) described neuronal cell loss and mineralization of the globus pallidus in SC patients. Neuman (personal communication) believed that iron accumulation was the most prominent abnormality in her SC brain collection, and Hopf (1952) correlated the presence of minerals with catatonic symptomatology. Furthermore, many neuroleptic drugs such as chlorpromazine chelate iron (Rajan et al. 1974; Ben-Shachar et al. 1985) and in chronic usage,

From the Clinical Brain Disorders Branch, National Institute of Mental Health, Bethesda, MD (M.F.C., C.M.P., I.W., B.I.K., B.S., D.R.W., J.B.K.) and the Department of Pathology and Neuropathology Laboratory, The Johns Hopkins University School of Medicine, Baltimore, MD (M.F.C.).
Address reprint requests to Manuel F. Casanova, M.D., Director of the Brain Bank Unit, Neurosciences Center at St. Elizabeths, 2700 Martin Luther King Jr. Avenue, Washington, DC 20032.
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increase iron concentration in the caudate nucleus (Drayer 1987). Recently, extensive "iron" pigment deposition in both basal ganglia and substantia nigra has been reported in a bipolar affective disorder patient with tardive dyskinesia due to haloperidol overdose (Campbell et al. 1985). Given the highly specific modulatory effect of iron over the dopamine D-2 receptor (Youdim et al. 1983), it seemed evident that further work in this area was necessary. In the present study, we used a LOATS computer image analysis system to quantify the amount of mineral visible on computerized tomographic (CT) scans of SC and control psychiatric patients. As this neuroimaging modality is noninvasive, it allows the examination of a larger series of patients than is possible in postmortem studies.

Methods

All CT scans obtained over a 3-year period at a general psychiatric hospital (St Elizabeths, Washington, DC) were reviewed for this study. Patients had been referred for CT scanning by their treating psychiatrists. Clinical diagnoses were determined by chart review and conform to DSM-III criteria. CT scans were performed without contrast enhancement on an EMI 1010 scanner. All films were performed at the same magnification, with window width and levels set by the technicians to observe maximum soft-tissue contrast. Three physicians (a radiologist, a neurologist, and a psychiatrist) independently read all scans for evidence of basal ganglia mineralization. CT scans demonstrating mineralization were analyzed with a computer image analysis system.

A LOATS computer image analysis system interfaced to a DAGE 68 camera was used to digitize CT scan films that were placed over a light box. The digitized image was then displayed on a monitor for further analysis (Loats et al. 1986). Software routines allowed for the calibration of illumination, objectives, and areas. All images were examined at 2.8 × magnification and 0.31 mm resolution. An index case where mineralization could be clearly distinguished was selected. The mineralized area was identified, enlarged ×4 and its transmission values were isolated using a boundary function. The resultant optical densities values were contrast adjusted to all gray levels (color steps) of the displayed image. Redigitization of the original scan with the new coloration scheme gave all pixels with an optical density range similar to the minerals. The overall pattern of mineralization on the computer-generated image was identical to that on the original scans while eliminating the rest of the brain (background). To normalize the remaining CT scans, the range of optical densities selected in the index case was divided by the reading obtained from the occipital bone near the inion. The transmission values for each scan were then adjusted to give the same ratio as in the index case when divided by the optical density reading of their occipital bone. The area of the scan covered by minerals was calculated by multiplying the square of the resolution by the number of pixels.

Results

A total of 725 CT scans were reviewed. The scans from two groups of patients were distinguished: those meeting DSM-III criteria for SC (275 patients) and those with other diagnoses (450 patients). Eighteen scans showed basal ganglia mineralization (2.5%): 7 were from schizophrenic patients (a prevalence of 2.6%) and 11 had other diagnoses (a prevalence of 2.4%). The SC patients were 53.4% ± 17.7 years of age (mean ± SD) and the nonSC patients were 73.5 ± 7.5 years of age (mean ± SD). All had multiple

Table 1. Data Profile on Patients With Basal Ganglia Mineralization

Diagnosis	Age	Gender	Race	Iron (mm^2) left basal ganglia	Iron (mm^2) right basal ganglia
SC	62	F	B	7.98	8.68
SC	61	F	B	1.61	0
SC	53	M	B	0.54	0.27
SC	23	M	B	0.51	0.24
SC	71	M	B	0	2.61
SC	36	F	W	1.96	3.22
SC	68	M	B	1.53	1.21
Bipolar disorder, manic	58	F	W	1.56	1.53
Major depression	74	F	B	1.13	2.42
Major depression	70	M	B	1.48	2.28
Dementia	80	F	B	4.06	5.46
Dementia	72	M	B	1.42	0.86
Dementia	67	M	B	0.24	1.02
Dementia	72	F	B	1.80	0.35
Dementia	72	M	B	0	1.93
Dementia	87	M	W	0.67	2.88
Dementia	77	F	B	2.88	1.72
Dementia	79	F	B	0	1.72

hospitalizations, received neuroleptic medications, and came from low socioeconomic backgrounds. Ten patients had a strong history of violent, uncontrollable behavior which led to hospitalization. Laboratory work-up for diseases associated with basal ganglia mineralization was unrevealing. One patient had elevated T4 levels, but other thyroid indices were normal. Revision of the records and/or patients' photographs revealed no evidence of cataracts, dry brittle nails, rough and puffy skin, sparce dry hair, or malformed teeth, as might be found in pseudohypoparathyroidism.

Four patients had abnormal involuntary movements: 1 had a family history of paroxysmal chorea, 1 had tardive dyskinesia, and 2 had tremors related to alcoholism. Six patients suffered from generalized seizures and were treated with anticonvulsants. Eight of the nonschizophrenic (nonSC) patients had a primary diagnosis of dementia (see Table 1). Eight of our nonSC patients exhibited psychotic symptoms. In 2 of these cases, psychosis was related to alcoholism or drug abuse, (PCP) and in 3 additional patients a diagnosis of schizophrenia had been considered at some point during hospitalization.

The increased frequency of mineralization of the basal ganglia in our sample was compared with the reported frequency in the general population by a series of chi-square tests. Our sample was significantly higher ($P < 0.001$) than those reported in previous CT studies (Koller et al. 1979; Murphy 1979; Sachs et al. 1979; Brannan et al. 1980; Harrington et al. 1981) with the exception of that found in the study of Puvanendran et al. (1982). However, the prevalence of basal ganglia mineralization in our SC and nonSC patients did not differ significantly from that reported in an unselected autopsy population (Wagner et al. 1955). A Pearson Product Moment Correlation was performed to investigate the possible relationship between amount of mineral and age. No significant correlation was found ($r = 0.105$, $p > 0.05$). A two-way analysis of variance (ANOVA) was performed to determine the possible effects of diagnosis and gender on total iron concentrations in the basal ganglia. No significant differences were noted ($F(17,3) = 2.00$, $p > 0.05$). An analysis of covariance (ANCOVA) was performed to determine the possible

effects of diagnosis and gender on mineral content in the basal ganglia controlling for the effects of age. No significant differences were noted ($F(17,3) = 0.09$, $p > .0.05$).

Analysis of standards of known size, visualized at the same magnification as the digitized CT scans, showed the technique used in this study permitted accuracy of area measurement within the 99% confidence limits.

Discussion

Iron and Minerals

The presence of iron in the brain is of special interest in schizophrenia as its accumulation closely parallels the distribution of dopamine (Youdim 1985). This can be attributed, in part, to the role played by iron as a cofactor of tyrosine hydroxylase (Youdim 1985), the rate limiting enzyme in the synthesis of catecholamines. The iron present in this enzyme, combined with that of heme and other storage compounds, comprise only a fraction of the total brain iron (Youdim 1985). In comparison, a large percentage of brain iron is observed microscopically as deposits in pallidal vessel walls and less frequently in the dentate nucleus of the cerebellum (Lowenthal and Bruyn 1968). Although these deposits have been variously named calcium, Spatz's pseudocalcium (Spatz 1922), and Bochnik's neurogel (Schiffer 1971), the exact composition remains uncertain. Classical histochemical analysis demonstrated the predominance iron in these deposits (Hurst 1926), but more recent studies using atomic absorption, infrared spectroscopy, potentiometry, and related techniques have shown, in addition, the presence of calcium, manganese, chlorine, aluminum, zinc, an organic matrix, and many other residues in different proportions (Smeyers-Verbeke et al. 1975).

Significance

The use of a LOATS computer image analysis system allows the quantification of minerals from CT scans. This permits analysis of a larger number of patients than is possible in postmortem studies, better correlation with clinical status, and the possibility of ongoing prospective analysis. Both our SC (2.6%) and nonSC (2.4%) groups showed a higher prevalence of basal ganglia mineralization than has been reported in CT surveys of the general population (0.33%–0.75%) (Koller et al. 1979; Murphy 1979; Sachs et al. 1979; Brannan et al. 1980; Harrington et al. 1981). This fact implies that the method used to detect basal ganglia mineralization in the present study was more sensitive than those of previous neuroimaging series which relied on earlier generation scanners. Therefore, a direct comparison with older neuroimaging studies is not warranted. A more meaningful comparison with postmorten series. In an unselected population consisting of 200 patients coming to autopsy, Wagner et al. (1955) found a 2% prevalence of basal ganglia mineralization. In this perspective, the prevalence found in the present series is unremarkable.

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