British Journal of Psychiatry (1984), **144**, 654–661

Evidence of Disturbed CSF Circulation and Brain Atrophy in Cases of Schizophrenic Psychosis

G. OXENSTIERNA, G. BERGSTRAND, L. BJERKENSTEDT, G. SEDVALL and G. WIK

Summary: The cerebrospinal fluid (CSF) circulation was studied with isotope cisternography in 30 patients with a schizophrenic type of psychosis. All had previously received neuroleptic treatment. Disturbed CSF circulation was found in 10 cases. In four of these, persistent intraventricular radioactivity was observed as well as partly obstructed CSF spaces. In the other six cases a slow CSF circulation was noted as well as evidence of partly obstructed CSF spaces especially of the upper posterior frontal region. Signs of atrophy of the cortex and vermis were found on CT scan in 10 cases. In four of these subjects a local atrophy was noticed in the upper posterior frontal cortex and around the frontal part of the interhemispheric fissure. Seventeen of the patients (57 per cent) had pathological findings at isotope cisternography and/or at CT. Disturbed circulation did not correlate with CT-findings, age, duration of psychosis, alcohol abuse, drug consumption or family history for psychosis. CT evidence of brain atrophy was significantly related to nonfamilial type of psychosis.

Psychotic manifestations in schizophrenia may be caused by alteration of brain function in one or several systems. Support for this hypothesis was originally claimed by Jacobi and Winkler (1927). Since the introduction of computed tomography (CT), several investigators have reported the occurrence of ventricular enlargement, cortical atrophy and vermis degeneration in some schizophrenic patients (Johnstone *et al*, 1976; Weinberger *et al*, 1979a; Weinberger *et al*, 1979b; Nybäck *et al*, 1982). A few investigators have reported negative findings (Glück, 1980; Benes *et al*, 1982; Weinberger *et al*, 1982). The cause of these changes in cerebral morphology and their relationship to the different aspects of schizophrenic symptomatology has not been clarified. Ventricular enlargement may be related to primary loss of cells within the brain or an alteration of fluid and pressure homeostasis within the cerebrospinal fluid (CSF) system. Accordingly disturbances in CSF circulation may be a pathophysiological mechanism that can result in the alteration of brain morphology in schizophrenic subjects. In recent studies, evidence was presented for a relationship between familial disposition for schizophrenia and high or deviant CSF concentrations of the major monoamine metabolites, 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) (Sedvall and Wode-Helgodt, 1980: Sedvall *et al*, 1980). The deviant monoamine metabolite concentrations may be due to a primary alteration of monoamine metabolism or an alteration of CSF circulation. Since both ventricular enlargement and deviant monoamine metabolite concentrations may be caused by an altered flow of CSF, we have studied the CSF circulation in schizophrenic patients using ^{111}In-DTPA.

The study aimed at discussing whether schizophrenic patients show evidence of a disturbed CSF circulation.

Method

The patients were recruited from the psychiatric clinics at the Karolinska and Beckomberga hospitals in Stockholm. They were selected on the basis of clinical evidence of schizophrenic type of psychosis, age range between 24 and 45 years, absence of neurological disorder and absence of manifest alcohol or drug abuse. Patients were diagnosed according to the Research Diagnostic Criteria for schizophrenia, RDC (Spitzer *et al*, 1978) as independently evaluated by two psychiatrists. The present study was performed on 33 patients with a schizophrenic type of psychosis. Three patients were excluded for technical reasons, in two cases because of leakage at the site of injection (Henriksson and Voigt, 1976). Of the remaining patients, 17 were men (age: mean 32 years, range 24–45) and 13 women (age: mean 35 years, range 25–44). Twenty six of the subjects fulfilled the RDC for schizophrenia. Two patients were schizoaffective, one had "other psychiatric disorder with schizophrenic features", and one had "unspecified functional psychosis—paranoid state". The duration of the disorder varied between one month and 25 years with a mean value of eight years.

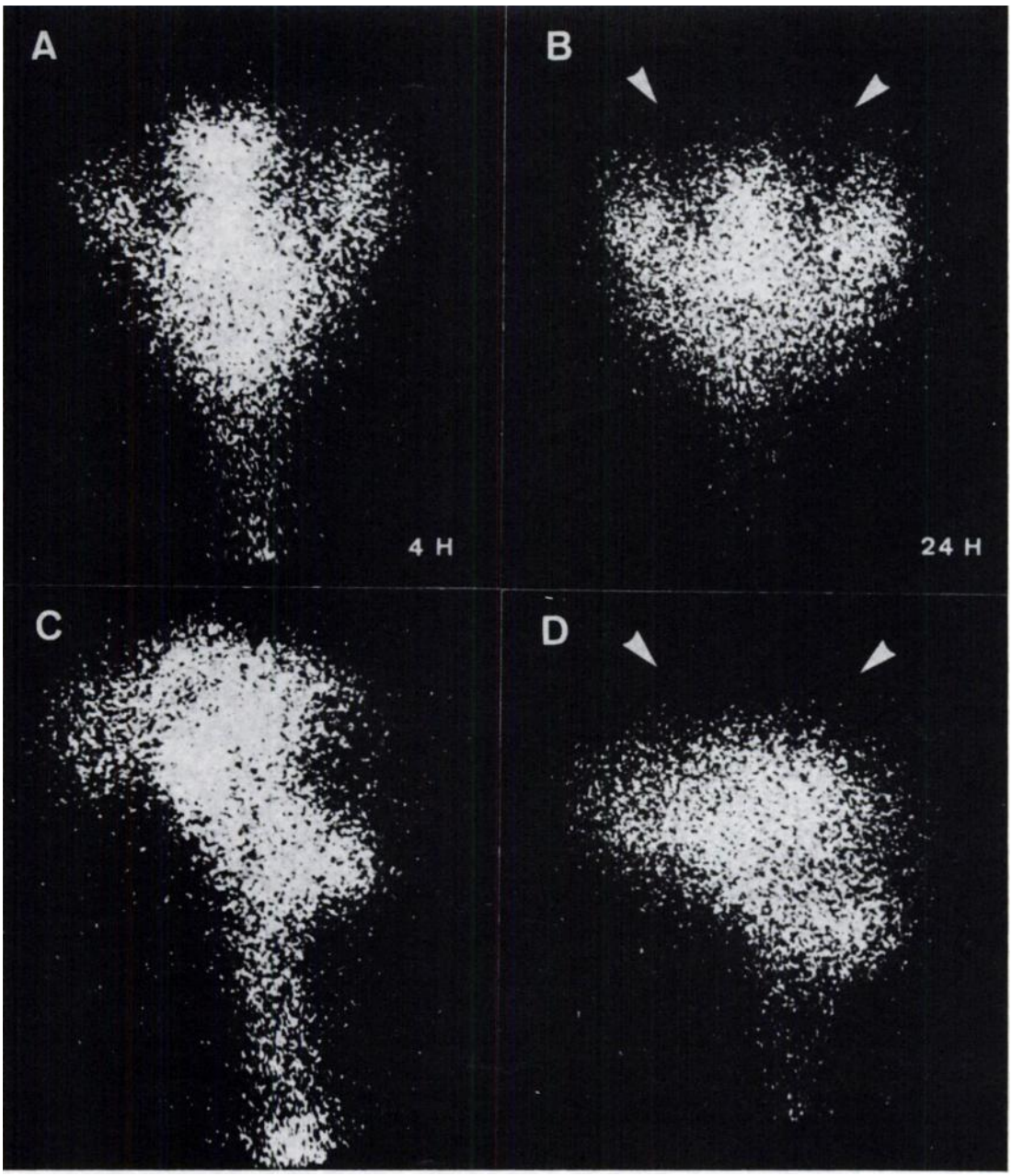

FIG 1.—Isotope cisternography after intrathecal administration of 18.5 MBq ^{111}In-DTPA. Frontal projections (A and B) after four and 24 hours respectively demonstrate intraventricular radioactivity (arrowheads) which persists after 24 hours (B). Bilateral obstruction of the CSF spaces over the hemispheres is also shown in the lateral projections after 4 (C) and 24 hours (arrowheads) (D).

https://doi.org/10.1192/bjp.144.6.654 Published online by Cambridge University Press

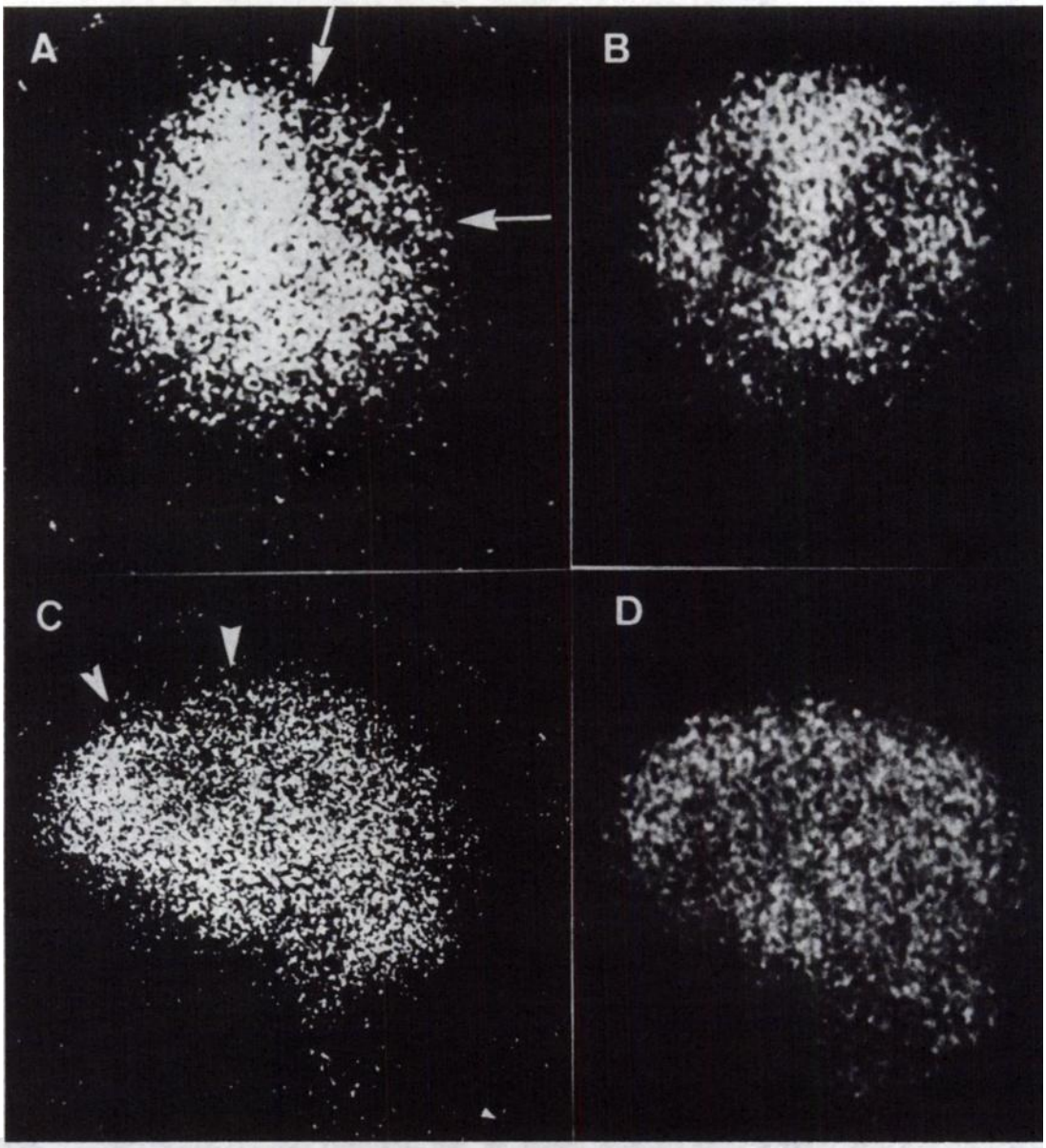

FIG 2.—Examples of local obstruction of the subarachnoidal space shown as defects in the distribution of radioactivity 24 hours after administration of the radionuclide. In (A) a region with low radioactivity over the left frontal lobe (arrows) is demonstrated. In (C) another patient with lack of radioactivity in the same region is demonstrated in lateral projection (arrowheads). (B) and (D) show the corresponding images of a normal case.

The patient records were examined in order to register somatic disorders and obstetric complications. EEG was recorded on all subjects.

The patients had previously received neuroleptic treatment with various compounds. Lifetime consumption of neuroleptics was determined for each subject using patient records. Doses were recalculated and expressed in chlorpromazine equivalents (Hollister, 1974). The consumption varied between 6 and 3979 grams chlorpromazine equivalents with a mean value of 716 grams. At the time of the investigations,

https://doi.org/10.1192/bjp.144.6.654 Published online by Cambridge University Press

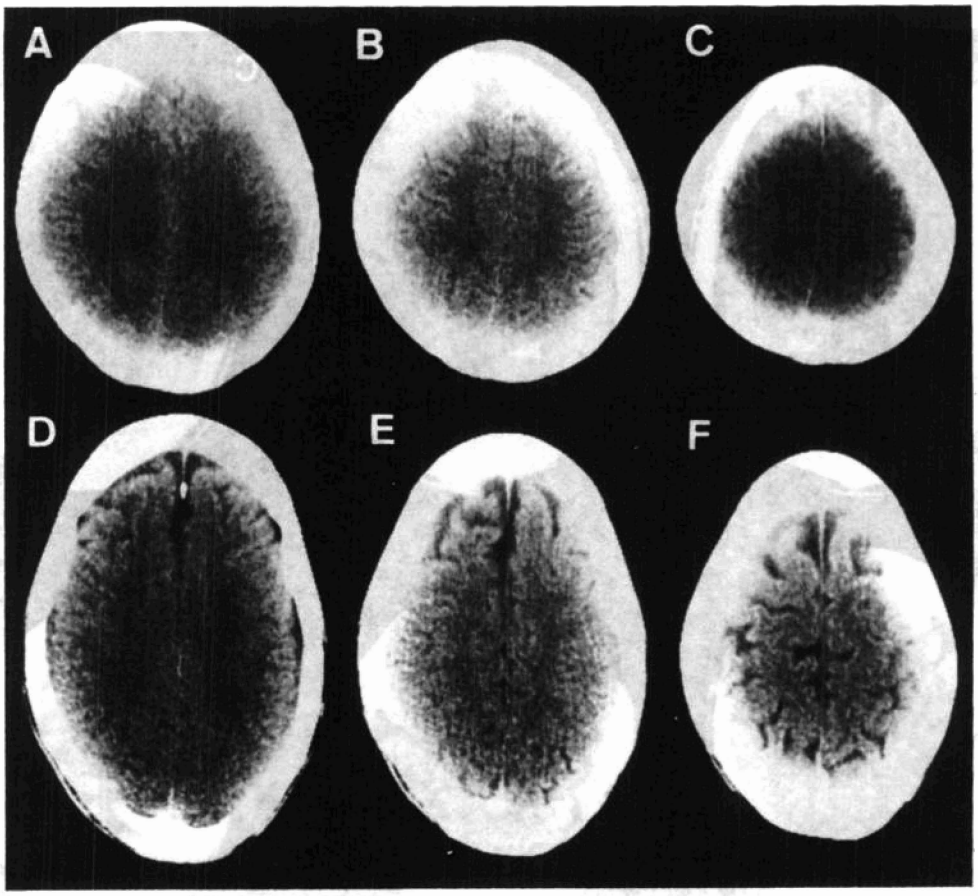

FIG 3.—CT scans demonstrating the upper frontoparietal regions in a normal 30 year old man (A-C) and the corresponding CT scans of a 27 year old schizophrenic patient (D-F) with wide frontal sulci and a wide frontal part of the interhemispheric fissure.

four subjects had been drug free for at least two weeks.

The patients were also classified with regard to family history for psychiatric disorder using the following method. The patient and a close relative were questioned if among the first and second degree relatives there were subjects who had been hospitalized for a psychiatric disorder. Parish registers were scrutinized in order to find all relatives up to the second degree. The information from the parish register gave information independent from the anamnestic data especially concerning suicide, psychosis and mental retardation. The hospital records for relatives having suffered from psychiatric disorder were collected. The examination of these records formed the basis for the classification of family history.

^{111}In-DTPA (18.5 MBq, 0.5 mCi) was injected intrathecally via the lumbar route. Pressure recording and Queckenstedt's test was routinely performed before the injection. A GE Maxi camera 400 T supplied with a medium energy collimator was used for picture recording 3, 6, 24 and 48 hours after administration of the radioactivity. In order to exclude leakage at the site of injection as a reason for a low intracranial accumulation of radioactivity, frontal and lateral images of the lumbar region were always taken. The subjects were fasting and had been on bedrest for eight hours prior to the examination. After injection of the radioactivity, the patients stayed recumbent for one hour. Later they were allowed to move around freely. Before the radioactivity was injected, between 8 and 9 a.m., 12.5 ml of CSF were sampled for biochemical analyses using precautions described by Sedvall *et al* (1980).

Concentrations of the major monoamine metabolites—HVA, 4-hydroxy-3-methoxyphenylethylene glucos (MOPEG) and 5-HIAA—were measured using GC/MS according to Swahn *et al* (1976). Protein was measured as described by Lowry (1951).

The patients were also studied with CT using a GE CT/T 8800 scanner. A slice thickness of 10 mm was used and no i.v. contrast was administered. The CT results were interpreted by two neuroradiologists. Morphologic changes such as hydrocephalus, wide hemispheric sulci and atrophic changes of the vermis were especially noted. Ventricular measure

https://doi.org/10.1192/bjp.144.6.654 Published online by Cambridge University Press

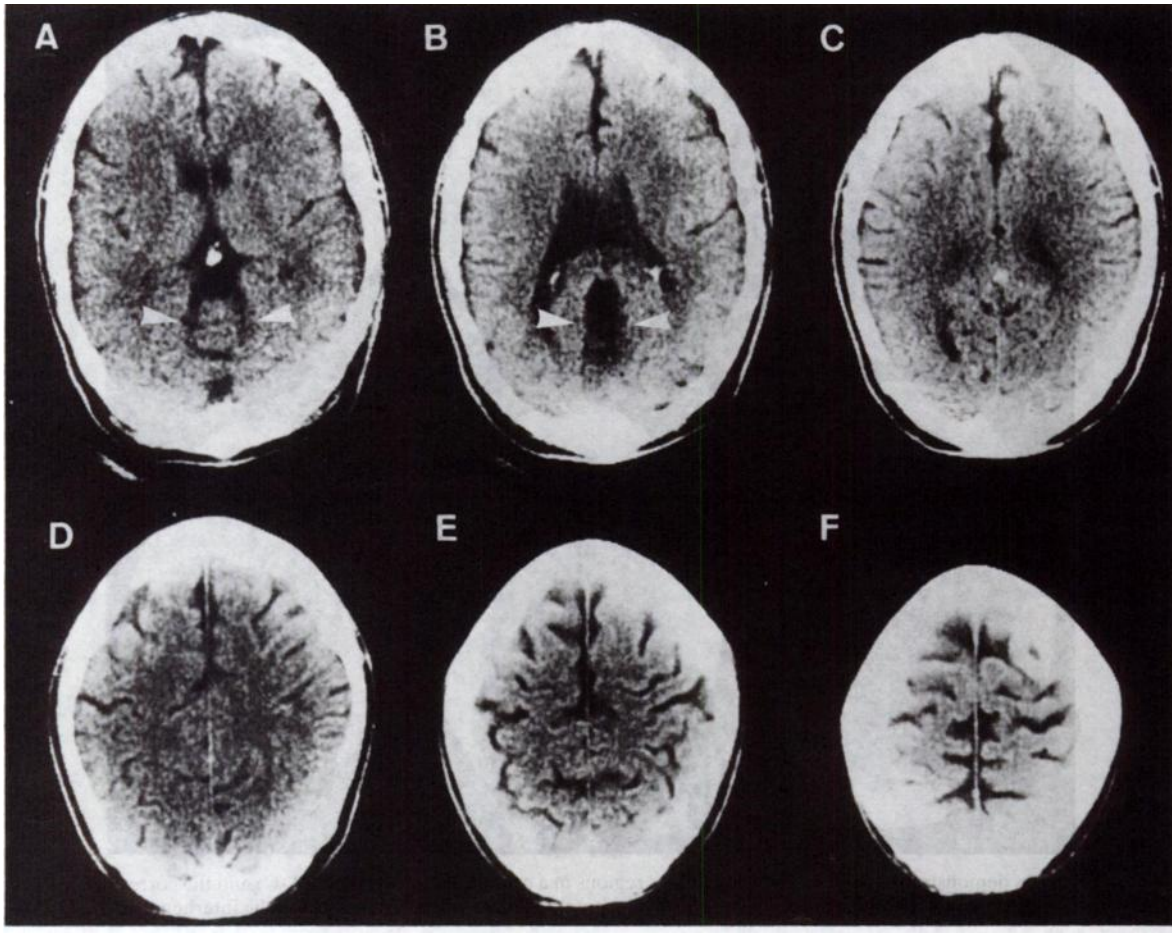

FIG 4.—CT scans demonstrating vermian atrophy (A) and wide CSF space above vermis (B) in a 38 year old schizophrenic man. In (D-F) wide parietal sulci are demonstrated in the same patient.

ments were also performed as described by Nybäck *et al* (1982).

Results

Isotope cisternography

Of the 30 patients, 20 (66 per cent) had a normal CSF circulation according to the isotope cisternography. Four patients had clear pathological findings consisting of persistent intraventricular radioactivity and a markedly reduced distribution of radioactivity over the hemispheres (Figure 1). These subjects were classified as severely pathological in the subsequent analyses. Six other patients had signs of a slow CSF circulation with a reduced accumulation of radioactivity over the convexity. The regions with evidence of a disturbed or blocked CSF circulation were located predominantly in the upper and posterior frontal region (Figure 2). These findings were classified as pathological.

Computed tomography

The CT studies were considered normal in 19 cases (63 per cent). In all the patients, the ventricular index was below 0.30 and the width of the third ventricle was less than 5 mm, which is considered to be in the normal ranges (Gyldenstedt, 1977). In 10 patients, atrophic changes were found. Four of these had clear changes consisting of wide hemispheric and interhemispheric sulci in the frontal region (Figure 3). The cortical sulci supratentorially were considered pathologically wide in four cases. Vermis atrophy (Figure 4) was found in six cases. A slight hydrocephalus was found in one case who also had persistent intraventricular radioactivity at isotope cisternography. One patient had small paraventricular calcifications of unknown ethiology.

Of the four patients with severely pathological CSF circulation, two had atrophic changes shown in CT, and the other two had normal CT scans. Four out of six patients with

https://doi.org/10.1192/bjp.144.6.654 Published online by Cambridge University Press

TABLE I
Relationship between brain atrophy and negative family history for schizophrenic psychosis

	No psychiatric family history	Family history for schizophrenic psychosis	
No atrophy	5	7	12
Atrophy	7	1	8
	12	8	20

Fisher's exact test = 0.05

pathological findings at isotope cisternography had normal CT examinations. Of the four patients with signs of frontal cortical atrophy, two had a normal and the other two a pathological CSF circulation.

Monoamine metabolites

The majority of the patients exhibited aberrant concentrations of monoamine metabolite concentrations in the CSF, as compared to values obtained in healthy volunteers. This was true for HVA, MOPEG as well as for 5-HIAA. Values were extreme in both directions. Since only four patients were drug free with regard to neuroleptic medication and all had received such medication for a substantial period, drug consumption is a highly confounding variable. There was no consistent relationship between monoamine metabolite concentrations, CSF circulation or atrophy. There tended to be a relationship between low HVA levels and brain atrophy ($P < 0.1$). The two patients who had the lowest HVA and 5-HIAA concentrations both had signs of a marked brain atrophy including atrophic changes in the vermis (Figure 4). None of these patients showed evidence of a disturbed CSF circulation. All the patients had a normal CSF protein concentration.

Family history

Adequate information concerning family history was obtained in 28 patients. Twelve of these patients had healthy relatives, eight subjects had relatives with schizophrenia or paranoid psychosis and of the remaining eight subjects, relatives had been treated for alcoholism, depression or suicide. There were no significant relationships between pathological CSF circulation and family history for schizophrenic type of psychosis. The occurrence of brain atrophy was significantly related to a form of schizophrenic psychosis that lacked family history for the disorder (Table I). Suicide and alcoholism also tended to occur in a higher frequency in the families of cases who lacked brain atrophy.

Clinical data and previous drug treatment

There were no significant relationships between pathological isotope cisternography or CT scans and duration of the disorder, duration of drug treatment, total neuroleptic consumption, somatic disorders, obstetric complications, cerebral trauma, previous alcohol or drug abuse or abnormal EEG recordings.

Discussion

CSF circulation has not previously been studied in schizophrenic patients or in healthy subjects. Although the technique used in the present investigation is indirect and semiquantitative it is an established method to diagnose disturbances of CSF circulation in patients with neurological and mental impairment (Lying-Tunell, 1977). The present investigation should be regarded as a first attempt to evaluate different aspects of CSF circulation in schizophrenia. We found evidence of pathological CSF circulation in a surprisingly high percentage (33 per cent) of young schizophrenic patients. Since all the patients had normal CSF pressure and normal Queckenstedt's test, the alteration of the CSF circulation was not related to high pressure hydrocephalus. In only one of the subjects, the CT scan demonstrated a slightly enlarged ventricular system, possibly due to low pressure hydrocephalus. The types of CSF circulation disturbances found in this patient group may be related to:

(a) reduced CSF production in the choroid plexus; or

(b) general or partial obstruction of CSF transport pathways.

Such alterations may be caused by genetic, infectious, traumatic or unknown mechanisms. In the present relatively small number of patients, no consistent relationship to family history for schizophrenia, obstetrical complications, cerebral trauma or meningoencephalitis was found.

Since all the patients had received previous neuroleptic treatment, a possible relationship to drug consumption was examined. An acute effect of neuroleptic treatment is unlikely. Thus in two patients who had pathological CSF circulation, neuroleptic treatment had been withdrawn for two and three weeks respectively. A chronic effect of neuroleptic treatment on the CSF circulation also seems unlikely since several patients who had a very high neuroleptic consumption, had a normal CSF circulation. The relationship between disturbed CSF circulation and the schizophrenia in these patients may be causal or unrelated. It is possible that a primarily altered CSF circulation affects neuronal function in a way that contributes to or directly causes the psychotic symptoms. It is well-known that several nutritional factors and waste products of brain metabolism are transported, at least partly, by means of the CSF (Cserr *et al*, 1975). If the disturbed CSF circulation is the cause of the psychosis, corrective measures aiming at improving CSF circulation may be attempted.

Several investigators have described signs of brain degeneration in schizophrenic patients on the basis of CT signs. This was definitively verified in this study as about 30 per cent of the patients showed evidence of brain atrophy. However, there was no statistical correlation between signs of atrophy and disturbed CSF circulation. Single patients had a marked distur-

bance of CSF circulation and a normal CT scan. Other patients had marked evidence of brain atrophy and a normal CSF circulation. These results indicate that brain atrophy and altered CSF circulation are unrelated and caused by different mechanisms, at least in some patients.

As found in previous studies (Sedvall and Wode-Helgodt, 1980; Wiesel *et al*, 1983), some patients in the present series had deviant concentrations of monoamine metabolites in lumbar CSF. Neuroleptic treatment is known to elevate the HVA concentrations in the CSF (Sedvall *et al*, 1975; Wode-Helgodt *et al*, 1977; Bjerkenstedt *et al*, 1977; Härnryd *et al*, 1984). Since most of the patients were receiving neuroleptic medication, the interpretation of the deviant values is complicated. In the present series of patients, there was no statistical relationship between disturbed CSF circulation and monoamine metabolite concentrations. Accordingly the study did not support the view that abberant monoamine concentrations in schizophrenic patients are related to a disturbed CSF circulation. Brain atrophy tended to be related to low concentrations of HVA in CSF (P 0.1). This tendency is in line with previous findings by Nybäck *et al* (1983), van Kammen *et al* (1983) and Potkin *et al* (1983). Thus the statistical analyses did not give significant evidence of a relationship between monoamine metabolite concentrations and brain atrophy or CSF disturbance in the total group of schizophrenic patients. However, single patients had such low HVA and 5-HIAA concentrations in relation to healthy volunteers that some relationship with the patients' psychotic symptoms cannot be excluded.

We found no relationship between disturbed CSF circulation and family history for psychosis. On the other hand, the occurrence of different types of brain atrophy was significantly related to nonfamilial forms of schizophrenia and paranoid psychosis. Only one patient out of eight with a familial form of schizophrenia exhibited brain atrophy. The schizophrenic patients who had evidence of brain atrophy (Table I) had an accumulation of nonfamilial forms of psychosis. This may be expected if the atrophy and possibly also the psychosis is caused predominantly by environmental influences on the brain like trauma, bleeding or infections during development.

For a more detailed evaluation of the functional and morphological findings obtained in this study, a group of healthy subjects is currently being studied with CT and isotope cisternography using 99mTc-DTPA according to Bergstrand *et al* (1982).

Conclusions

A substantial proportion of patients with psychosis of schizophrenic type have evidence of either a disturbed circulation of cerebrospinal fluid, or local or general brain degeneration. These different alterations of brain function and morphology do not seem to be correlated. The majority of cases with cerebral atrophy have a nonfamilial type of schizophrenia.

Acknowledgement

The authors express their sincere thanks to Gunnar Edman, Ph.D., for his great help with the statistical analyses.

This work has been supported by grants from the Swedish Medical Research Council (B83-21X-03560-12B), the Karolinska Institute and the Bergvall Foundation.

References

Benes, F., Sunderland, P., Jones, B. D., LeMay, M., Cohen, B. M. & Lipinsky, J. F. (1982) Normal ventricles in young schizophrenics. *British Journal of Psychiatry*, **141**, 90–3.

Bergstrand, G., Larsson, S., Bergström, M., Eriksson, L. & Edner, G. (1982) Cerebrospinal fluid circulation: Evaluation by single-photon and emission tomography. *American Journal of Neuroradiology*, **4**, 557–9.

Bjerkenstedt, L., Gullberg, B., Härnryd, C. & Sedvall, G. (1977) Monoamine metabolite levels in cerebrospinal fluid of psychotic women treated with melperone or thiothixene. *Archiv für Psychiatrie und Nerven-Krankenheiten*, **224**, 107–18.

Cserr, H., Fenstermacher, J. & Fencl, V. (eds.) (1975) *Fluid Environment of the Brain*. New York: Academic Press.

Glück, E., Radü, E. W., Mundt, C. & Gerhardt, P. (1980) A computed tomographic prolective trohoc study of chronic schizophrenics. *Neuroradiology*, **20**, 167–71.

Gyldenstedt, C. (1977) Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. *Neuroradiology*, **14**, 183–92.

Henriksson, L. & Voigt, K. (1976) Age-dependent differences of distribution and clearance patterns in normal RIHSA cisternograms. *Neuroradiology*, **12**, 103–7.

Hollister, L. E. (1974) *Clinical Use of Psychotherapeutic Drugs*. Springfield, Illinois: Charles C. Thomas.

Härnryd, C., Bjerkenstedt, L., Gullberg, B., Oxenstierna, G., Sedvall, G. & Wiesel, F.-A. (1984) Time course for effects of sulpiride and chlorpromazine on monoamine metabolite and prolactin levels in cerebrospinal fluid from schizophrenic patients. *Acta Psychiatrica Scandinavica*, Suppl. 311, **69**, 75–92.

Jacobi, W. & Winkler, H. (1927) Encephalographische Studien an Chronisch Schizophrenen. *Archiv für Psychiatrie und Nervenkrankenheiten*, **81**, 299–332.

Johnstone, E. C., Frith, C. D., Crow, T. J., Husband, E. J. & Kreel, L. (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, **II**, 924–6.

VAN KAMMEN, D. P., MANN, L. S., STERNBERG, D. E., SCHEININ, M., NINAN, P. T., MARDER, S. R., VAN KAMMEN, W. B., REIDER, R. O. & LINNOILA, M. (1983) Dopamine-beta-hydroxylase activity and homovanillic acid in spinal fluid of schizophrenics with brain atrophy. *Science*, **220**, 974–6.

LOWRY, O. H., ROSEBROUGH, N. J., FARR, A. L. & RANDALL, R. J. (1951) Protein measurement with the Folin phenol reagent. *Journal of Biological Chemistry*, **193**, 265–75.

LYING-TUNELL, U. (1977) Cerebrospinal fluid turnover and convexity block in mental impairment. *Neurology*, **27**, 460–70.

NYBÄCK, H., WIESEL, F.-A., BERGGREN, B.-M. & HINDMARSH, T. (1982) Computed tomography of the brain in patients with acute psychosis and in healthy volunteers. *Acta Psychiatrica Scandinavica*, **65**, 403–14.

—— BERGGREN, B.-M., HINDMARSH, T., SEDVALL, G. & WIESEL, F.-A. (1983) Cerebroventricular size and cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy volunteers. *Psychiatry Research*, In press.

POTKIN, S. G., WEINBERGER, D. R., LINNOILA, M. & WYATT, R. J. (1983) Low CSF 5-hydroxyindoleacetic acid in schizophrenic patients with enlarged cerebral ventricles. *American Journal of Psychiatry*, **140**, 21.

SEDVALL, G., FYRÖ, B., GULLBERG, B., NYBÄCK, H., WIESEL, F.-A. & WODE-HELGODT, B. (1980) Relationships in healthy volunteers between concentrations of monoamine metabolites in cerebrospinal fluid and family history of psychiatric morbidity. *British Journal of Psychiatry*, **136**, 366–74.

—— & WODE-HELGODT, B. (1980) Aberrant monoamine metabolite levels in CSF and family history of schizophrenia. *Archives of General Psychiatry*, **37**, 1113–6.

—— ALFREDSSON, G., BJERKENSTEDT, L., ENEROTH, P., FYRÖ, B., HÄRNRYD, C., SWAHN, C.-G., WIESEL, F.-A. & WODE-HELGODT, B. (1975) Selective effects of psychoactive drugs on levels of monoamine metabolites and prolactin in cerebrospinal fluid of psychiatric patients. In *Proceedings of the Sixth Int. Congress of Pharmacology*, **3**, 255–67.

SPITZER, R. L., ENDICOTT, J. & ROBINS, E. (1978) *Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders*. New York: Instrument No. = 59.

SWAHN, C.-G., SANDGÄRDE, B., WIESEL, F.-A. & SEDVALL, G. (1976) Simultaneous determination of three major monoamine metabolites in brain tissue and body fluids by a mass fragmentographic method. *Psychopharmacology*, **48**, 147–52.

WEINBERGER, D. R., TORREY, E. F., NEOPHYTIDES, A. N. & WYATT, R. J. (1979a) Lateral cerebral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry*, **36**, 735–9.

—— —— —— —— (1979b) Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. *Archives of General Psychiatry*, **36**, 935–9.

—— DELISI, L. E., PERMAN, G. P., TARGUM, S. & WYATT, R. J. (1982) Computed tomography in schizophreniform disorder and other acute psychiatric disorders. *Archives of General Psychiatry*, **39**, 778–83.

—— —— HERLOFSON, J., HÄRNRYD, C., NYBÄCK, H., OXENSTIERNA, G. & SEDVALL, G. (1983) Psychiatric morbidity within the family and steady state levels of CSF monoamine metabolites. In *Proceedings of the 5th Catecholamine Symposium in Gothenburg, Sweden, June 12–16, 1983* (ed. E. Usdin). New York: Alan R. Liss, Inc.

WODE-HELGODT, B., FYRÖ, B., GULLBERG, B. & SEDVALL, G. (1977) Effects of chlorpromazine treatment on monoamine metabolite levels in cerebrospinal fluid of psychotic patients. *Acta Psychiatrica Scandinavica*, **56**, 129–42.

Gustaf Bergstrand, M.D., *Department of Neuroradiology, Karolinska Institute*

Lars Bjerkenstedt, M.D., *Department of Psychiatry and Psychology, Karolinska Institute*

*Gabriella Oxenstierna, M.D., *Department of Psychiatry and Psychology, Karolinska Institute*

Göran Sedvall, M.D., *Chairman, Department of Psychiatry and Psychology, Karolinska Institute*

Gustav Wik, M.D., *Department of Psychiatry and Psychology, Karolinska Institute*

Karolinska Hospital, P.O. Box 60500, S-104 01 Stockholm, Sweden

*Correspondence

(Received 18 October; received 23 November 1983)