Brain Stem Encephalitic Lesions and Schizophrenia

A REPORT OF 3 CASES

M. FISMAN

SUMMARY

Three cases with schizophrenic/schizophreniform psychosis are described. Encephalitic-type lesions were found in the brain stem on histological study, in all cases. The possible relationship of the encephalitic lesions to the development of schizophrenia is discussed. Further research on a larger scale is suggested.

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Schizophreniform syndromes due to a variety of pathological lesions in various parts of the brain have been described.[1] Recently a viral basis for schizophrenia has been suggested,[2] and the same authors suggest that further clinical, epidemiological and pathological material should be accumulated to assess the validity of this hypothesis. The following 3 cases evidenced a schizophrenic/schizophreniform psychosis during life and exhibited evidence of encephalitic-type lesions on pathological study.

CASE 1

This patient was admitted to Tara Hospital in 1952 at the age of 21 years. Physical and neurological examinations were normal. He expressed the belief that he would develop into a supernaturally strong person and had made calculations that convinced him that he was identical with Jesus Christ and God. He felt within himself the power to perform miracles after the manner of Christ. He was solitary and preoccupied, and would stare vacantly into space. Nevertheless, he was correctly orientated in all modalities, and denied hallucinations.

The history revealed that the patient's birth and childhood were normal. His parents and an only sibling were all well. A paternal uncle however, was institutionalised for a similar nervous illness. The patient did well both scholastically and on the sportsfield. He was a prefect and *Victor Ludorum*, and matriculated at the age of 17 years. There was no evidence of premorbid schizoid personality. During his last year at school, a falling-off in his schoolwork was noted. During his first year at university he became asocial, showed thought disorder and developed a grandiose delusional system. He felt that he was Christ and visited the Bishop of Cape Town to announce this. Grandiose delusions of wealth were also present.

High-dosage insulin treatment was given, but the disease did not remit and the patient was unable to cope with jobs that he attempted, first working in an architect's office and then as a bank clerk. At this stage he was admitted to Tara. Further high-dosage insulin coma was given without success. The patient was discharged in 1953. An unsuccessful bilateral leucotomy was performed between 1953 and 1955.

In 1955 the patient was admitted to Weskoppies Mental Hospital. Physical and neurological examinations were normal and a blood Wassermann test was negative. The patient presented essentially as before. He was devoid of insight and deluded. He admitted to auditory hallucinations, hearing the voice of his girlfriend talking to him. Emotional blunting was present and at times the patient would assume catatonic postures. He had developed seizures following leucotomy and these were treated with phenobarbitone and Epanutin. The patient deteriorated over the ensuing years and by 1964 was disorientated for time and place. He was tried on a variety of psychotropic medication to no avail. In August 1973 he developed a pyrexial illness which was diagnosed as pneumonia. He died 5 days after the onset of this illness.

Autopsy

A full postmortem examination was performed within 24 hours of death. The body was that of a well-nourished, White male. A marked bilateral bronchopneumonia was present. Bilateral frontal burr-holes were noted and leucotomy entry sites on the superior aspect of the frontal lobes. The brain weighed 1 350 g and the vessels at the base showed mild atheroma. No abnormality was noted on sectioning the brain, other than the leucotomy pathway.

Histological examination of the lungs showed evidence of an aspiration bronchopneumonia. The liver showed congestion and periportal infiltration. Routine sections were taken from the frontal, parietal, occipital and temporal cortex, the hippocampus, lenticular nucleus, striatum, thalamus, hypothalamus and cerebellum. Semiserial sections of the brain stem were done, Sections were also taken from the leucotomy pathway. Neurons showing ischaemic change and an increase of lipofuscin were present in most areas. The meninges were thickened and marked gliosis was present at the leucotomy site, and some loss of Purkinje cells was evident in the cerebellum.

Department of Neuropathology, South African Institute for Medical Research, Johannesburg
M. FISMAN, M.B. B.CH., D.P.M.

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Examination of the brain stem sections showed neuroaxonal dystrophy in the nucleus gracilis, and an area of focal rarefaction and perivascular cuffing in the nucleus tractus spinalis trigemini oralis (Figs 1 and 2). Atrophy of the lateral segment of the superior olivary nucleus was present.

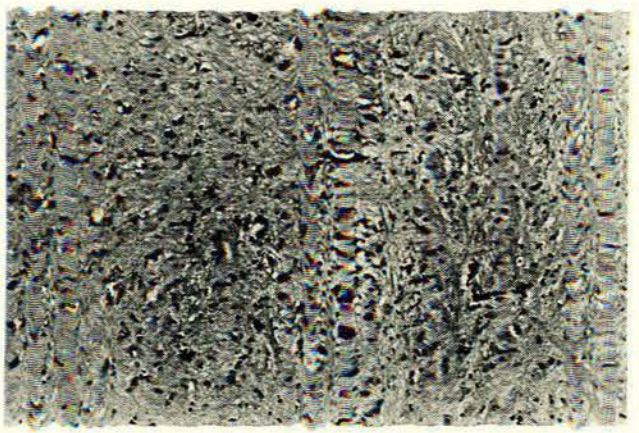

Fig. 1. Area of rarefaction in trigeminal nucleus (H. and E. × 95).

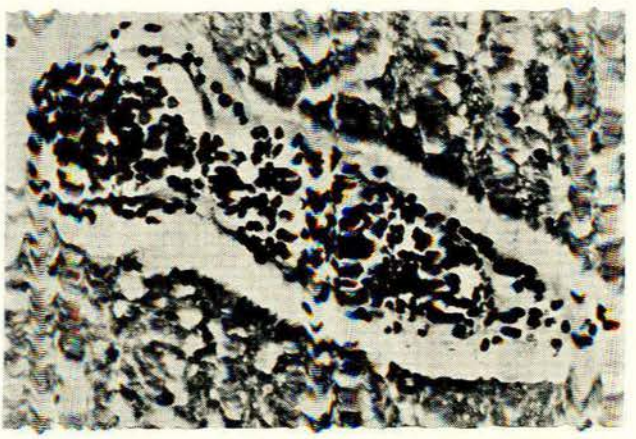

Fig. 2. Perivascular round cell infiltration of vessel in the spinal tract of the trigeminal nucleus (H. and E. × 375).

CASE 2

The patient was first admitted to Weskoppies Mental Hospital in November 1958. He was 36 years old, separated from his wife and working as a farmer. At this stage he was hallucinated and deluded, but fully orientated for time and place. He had attempted suicide at the prompting of the voice that he heard, and his delusions were of a persecutory nature. Physical examination did not reveal any abnormality; the patient was diagnosed as suffering from schizophrenia and treated on high doses of Largactil. He improved sufficiently to be discharged into the care of his father in 1959.

There were readmissions in 1959 and 1964, following failure to take his medication. The presenting features were essentially similar to those on his first admission except for the development of headaches for which the patient took phenacetin-containing preparations. Clinical examination, urinalysis, cerebrospinal fluid examination and tests for syphilis were all negative. In 1973 a grand mal seizure was recorded and within 9 months the patient was admitted in uraemia. He died 4 days after admission.

Autopsy

A full postmortem examination was performed within 24 hours of death. The body was that of an emaciated, middle-aged White male. Purpuric areas were present over the abdomen and arms. There was left ventricular dilatation and pulmonary oedema. The kidneys were smooth and shrunken with a decrease in the corticomedullary ratio and haemorrhage into the right renal pelvis. The brain appeared normal macroscopically and weighed 1 720 g. There was minimal atheroma of the vessels of the circle of Willis and of the vertebrobasilar system.

Microscopy revealed pulmonary oedema and congestion and the features of an analgesic nephropathy. Routine sections from cerebral and cerebellar cortex, basal ganglia thalamus and hypothalamus revealed many neurons showing ischaemic change and others filled with lipofuscin. Semiserial sections of the brain stem revealed lesions of the left trigeminal nucleus extending from the nucleus nervi trigemini sensibilis principalis orally, to the nucleus tractus spinalis trigemini caudalis caudally. The lesions were composed of microglial cells and were associated with neuronal loss (Fig. 3). Perivascular round cell infiltration was present orally and the lesion reached its maximum diameter at the level of the nucleus tractus spinalis trigemini oralis. Other findings in the brain stem were an apparent loss of nerve cells of the lateral segment of the nucleus olivaris superior and a perivascular round

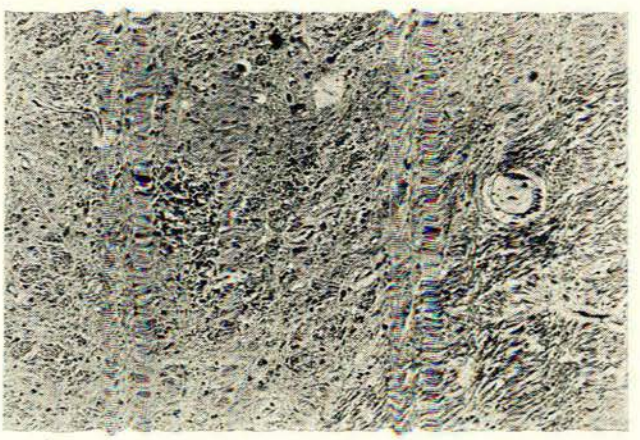

Fig. 3. Section demonstrating glial knot and neuronal loss as well as perivascular infiltrate (H. and E.)

cell infiltrate affecting a vessel supplying the nucleus gigantocellularis.

CASE 3

The patient was born in 1918. At the time of certification in 1935 he was an orphan, with an only brother who was serving in the air force. No information about the patient's delivery, childhood milestones or infections was available.

Grand mal seizures started when the patient was 11 years old. These became more severe and he left school at the age of 16 years because of the seizures. He then worked at Craighall Epileptic Gardens. Here he was found to be rather aggressive, and after assaulting a supervisor he was referred to the Johannesburg General Hospital, where he was certified. He was seen by 2 senior neurologists, but the examination did not reveal any focal abnormality and he was certified as an aggressive epileptic. No evidence of psychosis, dementia or deterioration was found at this stage, the patient being well orientated and having a good memory. A seizure was witnessed and described as generalised, associated with urinary incontinence, and followed by a period of confusion for which the patient was amnesic. The patient could apparently anticipate the seizure coming on, but was unable to describe this feeling. The patient was admitted to Weskoppies Mental Hospital, where he was found to be non-certifiable. He was persuaded to remain on as a voluntary boarder.

The next 10 years showed a gradual decline in the patient's mental status, despite a decrease in frequency of seizures. He was irritable, sullen and destructive and showed a marked religiosity. He remained correctly orientated in all spheres. His blood Wassermann test was negative.

In 1945 the first evidence of thought disorder and minor eccentricity was noted. By 1948 the patient admitted to hearing the voice of God and a year later he was using neologisms. In 1950 the first delusions presented, and by 1957 the patient had a fully-fledged delusional system. He felt that he was sent to hospital by God to do duty as a Pope. The other patients were nasty and interfering because they were jealous of him, and he only had seizures when God wished to punish him.

His condition remained static for the next 10 years, but thereafter there was a further deterioration with disorientation, perseveration, lack of volition and 'perverse' sexual tendencies. The patient died suddenly in October 1973.

Autopsy

A limited postmortem examination was performed, and only the brain was removed. The brain showed mild atrophy and weighed 1 300 g. The vessels at the base of the brain showed mild atheroma. No abnormality was found on section of the cerebrum, but section of the cerebellum revealed a haemorrhagic area in the central white matter.

Routine sections were taken from the frontal, parietal, occipital and temporal cortex, the hippocampus, lenticular nucleus, striatum, thalamus, hypothalamus and cerebellum. Semiserial sections of the brain stem were done.

Areas of ischaemic change were found in the cortex. Pseudocalcification of vessels supplying the lenticular nucleus was present and the vessels generally showed a mild sclerosis. An abundance of corpora amylacea was present in most areas studied, as well as lipofuscin-containing neurons. Sections from the temporal lobe showed prominent glia and gliosis of layer 1. Microscopic examination of the cerebellar lesion revealed a telangiectatic malformation. An area of perivascular round cell infiltrate was found in the parietal lobe. A glial knot and perivascular cuffing was found in the nucleus tractus spinalis trigemini interpolaris (Figs 4 and 5) and also in the nucleus centralis superior. The lateral segment of the nucleus olivaris superior showed atrophy. Neuro-axonal dystrophy was present in the tractus nervi trigemini spinalis and also in the nucleus gracilis.

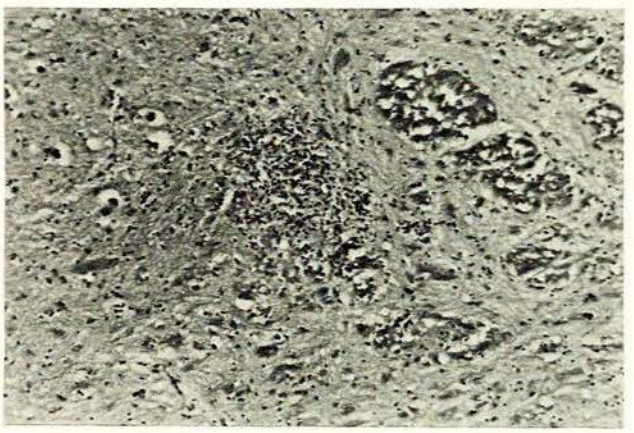

Fig. 4. Glial knot and neuronal loss in trigeminal nucleus of case 3 (H. and E. × 95).

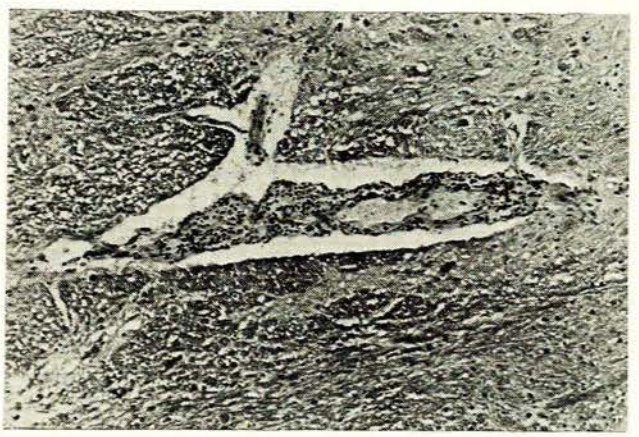

Fig. 5. Section showing marked perivascular cuffing of vessel supplying the trigeminal nucleus (H. and E.)

DISCUSSION

Two of the patients presented, and were diagnosed, as schizophrenic. The third presented initially with epilepsy,

but 16 years after the onset of epilepsy and 10 years after certification he developed a full-blown schizophreniform psychosis. This series of cases is unusual in that the schizophrenics developed epilepsy, one on a post-leucotomy basis and the other presumably on a uraemic basis. This atypical aspect of the material should be borne in mind when evaluating the pathological findings. All three patients presented with evidence of encephalitis affecting mainly the trigeminal nucleus, but also affecting other areas of the brain stem and brain. Another feature common to all the patients was atrophy of the lateral part of the superior olivary nucleus.

The viral theory of schizophrenia has been reviewed by Fuller and Peterson.[2] The findings in these three cases of perivascular cuffing, glial knots and areas of rarefaction necrosis are suggestive of viral infection. The distribution of the lesions is suggestive of a herpetic type lesion. Thus Bethlem[3] has described lesions in the trigeminal nucleus in a patient who had herpes zoster of the ear and face. Lesions are also found in this region in the brain stems of simians affected by B virus[4] (herpes simiae). In addition Cleobury *et al.*[5] have reported elevated levels of antibody to herpes simplex in serum from aggressive psychopaths and other psychiatric cases.

These 3 postmortem examinations were part of a series of 16 performed on White South Africans between 11 December 1972 and 3 October 1973, and were the only schizophrenic/schizophreniform cases. The remaining 13 cases were composed of 2 cases of Alzheimer's disease, 3 of senile psychosis, and one each of Huntington's chorea, subacute sclerosing encephalitis, anoxic encephalopathy (possibly carbon monoxide), carcinoma of the bronchus with secondaries in the brain, epilepsy without psychosis, Korsakoff's psychosis, manic-depressive disease and cerebrovascular disease. None of these 13 cases showed the distribution of encephalitic lesions present in the brain stems of the schizophrenics. It would therefore be tempting to assume that the encephalitic lesions present in the latter are significant, and indicate an underlying viral aetiology of schizophrenia. There are other features, however, that differentiate the schizophrenic group from the rest, and the encephalitic lesions may be a consequence of these associated conditions, rather than the cause of the schizophrenia.

The schizophrenic/schizophreniform group is distinguished by chronicity and long periods of institutionalisation. The encephalitis may therefore be a function of the duration of institutionalisation. It is relevant to indicate at this stage that of the 21 postmortem examinations described by Head and Campbell[6] in their classical monograph on the pathology of herpes zoster, 13 cases were from mental hospitals. There also appears to be a relationship between the presence of herpes virus antibody and environment.[7] Alternatively the presence of encephalitic lesions may indicate a proneness or predisposition for epileptic patients to develop this type of infection or lesion.

Nevertheless, because of the sharp difference between the schizophrenic and non-schizophrenic groups, it is felt that these findings offer some support to the viral hypothesis of schizophrenia. A problem is the differentiation of true schizophrenia from a schizophreniform psychosis. According to this argument, the above cases would be classified as schizophreniform psychoses of encephalitic aetiology, although, if postmortem examinations had not been performed on cases 1 and 2, they would have fallen into the category of true schizophrenia. Davison and Bagley[1] point out that this problem is mainly a semantic one, which can be bypassed by saying that the organic psychosis is phenomenologically indistinguishable from psychosis occurring in the absence of detectable organic brain disease. Their statement highlights the problem of the detectability of lesions in the brain. It should be pointed out that an average of 90 - 100 sections per brain stem were studied in the above cases, and that in 2 cases brain stem lesions were only elucidated on studying further sections. This would appear to be the minimum number of sections needed to ascertain the presence of these lesions.

Further work on a larger sample of schizophrenics and controls is needed to assess the nature and incidence of these lesions in the schizophrenic brain stem.

REFERENCES

1. Davison, K. and Bagley, C. R. *in* Herrington, R. N., ed. (1969): Brit. J. Psychiat. Special Publication No. 4, p. 113.
2. Fuller, T. E. and Peterson, M. R. (1973): Lancet, **2**, 22.
3. Bethlem, J. (1962): Acta Neuropath. (Berl.), **2**, 107.
4. Nieberg, K. C. and Blumberg, J. M. *in* Minckler, J., ed. (1972): *Pathology of the Nervous System*, vol. 3, pp. 2269 - 2323. New York: McGraw Hill.
5. Cleobury, J. F., Skinner, G. R. B., Thouless, M. E. and Eildy, P. (1971): Brit. Med. J., **1**, 438.
6. Head, H. and Campbell, A. W. (1900): Brain, **23**, 353.
7. Leading Article (1971): Brit. Med. J., **1**, 418.