Diencephalic amnesia: a reappraisal

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SYNOPSIS The anatomical basis of memory disorder related to lesions of the diencephalon is a controversial matter. A study of a patient who developed severe amnesia in association with bilateral metastatic tumour invasion of the medial and posterior thalamus is reported. The findings in this case have led to further discussion of this unsettled issue.

Lesions surrounding the floor and walls of the third ventricle have long been associated with the occurrence of amnesic states of the Korsakoff type. Although a number of anatomical structures have been implicated, most attention has been given to lesions of the mammillary bodies and/or its connections (Gamper, 1928; Hécaen and de Ajuriaguerra, 1956; Delay and Brion, 1958; Delay *et al.*, 1964; Kahn and Crosby, 1972) as the source of memory disturbance in disease affecting the diencephalon. Malamud and Skillicorn (1956), and, more recently, Victor *et al.* (1971) emphasized the importance of thalamic pathology in the pathogenesis of Korsakoff's psychosis. The latter authors, on the basis of an extensive pathological study of 82 patients with the Wernicke-Korsakoff syndrome, concluded that lesions in the medial dorsal nucleus of the thalamus, bilaterally, were critical anatomical substrata for the amnesia of this disorder. Their position is controversial and the significance of the thalamic lesions remains unsettled.

We have studied and will report a 64 year old, non-alcoholic man who abruptly developed amnesia as the presenting feature of an illness related to tumour invasion of the structures surrounding the posterior portion of the third

ventricle and upper brain-stem. The mammillary bodies, mammillothalamic tracts, and the anterior thalamus were spared. The findings in this case have prompted a review and reappraisal of the anatomy of amnesia associated with diencephalic lesions.

CASE REPORT

A 64 year old contractor was admitted to the Boston Veterans Administration Hospital for evaluation of his behaviour. A few days earlier, while walking with his son, the patient momentarily slumped to his knees. There was no loss of consciousness but immediately afterwards he was briefly 'disoriented and confused'. For the remainder of the day his gait was somewhat slow and unsteady but he continued his usual activities and appeared to be in good contact with his family. The following day, however, while attending a wedding with his wife, he complained of feeling ill and asked to go home. He then proceeded to drive to a house the family had moved from about 4½ years previously. When confronted with his error, he adamantly insisted that it was his home. When directed to his current home, he failed to recognize it. Ordinarily a quiet and polite individual, he had become obstinate, abusive, and sexually provocative. Because of this behaviour, the patient was referred to the Providence Veterans Administration Hospital, was evaluated by one of us (W.J.M.), and was transferred to the Neurobehavioral Center of the Boston Veterans Administration Hospital for further study.

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FIG. 1 *Lateral view of pneumoencephalogram with the patient in the upright position revealing a rounded mass which obliterates the posterior third ventricle.*

Admission examination revealed a well-developed, well-nourished right-handed man without significant abnormalities on physical examination. Blood pressure was 120/70 mmHg in both arms and the pulse was regular. The patient was alert and generally cooperative but mildly inattentive. Memory testing showed the most significant abnormalities. He consistently recalled five digits presented serially, but could not recall six. In testing his ability to learn new material, he could not remember the examiner's name despite frequent reminders and failed to recall any of three words five minutes after they had been taught. He was totally disoriented to time and place and was unable to give any details of his activities in the days preceding admission to the hospital. Recall for remote events was also impaired as he could not state his wedding date, the year he entered military service, details of his past medical history, or major public events occurring during his life. Similarly, he had considerable difficulty in manipulating old knowledge. Thus, relatively simple arithmetical problems such as change making and subtraction—for example, 100 minus 72—were failed. He could interpret simple proverbs adequately, but produced concrete responses when moderately difficult proverbs were offered. In contrast, language testing was essentially normal. His speech was fluent, there was excellent comprehension of spoken language, and

FIG. 2 *Coronal section of the cerebrum at the level of the posterior third ventricle showing the midline tumour mass. A small tumour implant can be seen in the floor of the left temporal horn (right side of photograph), not involving the hippocampal formation.*

both repetition and naming ability were normal. He could read and write at a level consistent with his high school education and could copy drawings, including three-dimensional figures, adequately. Motor praxis, right-left orientation, and finger recognition were within normal limits. There was a total lack of insight into his present disability. With only mild provocation he would break into tears and atypical laughter was noted several times. A report from the family revealed that on the day before admission the patient had failed to recognize his son until the son spoke to him.

The rest of the neurological examination demonstrated very little abnormality. There was some tendency for extinction of right-sided visual and auditory stimuli on double simultaneous stimulation, but no primary visual or tactile loss could be demonstrated. The extraocular movements were intact, there was no nystagmus, the fundi appeared normal, and visual acuity was within normal limits. The motor examination was normal except for an unsteady and somewhat wide-based gait. The reflexes were within normal limits and the toe signs were plantar.

Routine laboratory studies were all normal but a chest radiograph revealed a 3 × 3 cm circular mass in the left mid-lung zone. An electrocardiogram was interpreted as consistent with an old anteroapical myocardial infarction. A radioisotope brain scan was normal but an EEG contained bilateral paroxysmal delta activity, occurring independently on both sides with greater slowing in the anterior quadrants of the scalp. Lumbar puncture yielded clear colourless fluid under normal pressure which contained 0.14 g/l of protein and 4.9 mmol/l of glucose. Radiographs of the skull were within normal limits.

The patient's condition remained stable for a number of days but within a week after admission he had become considerably more drowsy and inattentive. Grasp reflex was then noted bilaterally and sucking and rooting reflexes were present. The plantar response on the left side became extensor. A cytological specimen from the lung mass was obtained by bronchoscopy and confirmed the diagnosis of bronchogenic carcinoma. Two weeks after admission he lapsed into a deep stupor, responding only slightly to massive stimulation such as bronchial suction. His pupils became unresponsive to light but remained equal, although changing in size over a period of time. A right carotid arteriogram demonstrated ventricular dilatation with slight stretching and flattening of the internal cerebral vein and was consistent with a mass in the pineal region. A pneumoencephalogram demonstrated a well-circumscribed rounded mass obliterating the posterior portion of the third ventricle (Fig. 1).

A ventriculoperitoneal shunt was placed and the patient's level of consciousness improved. He began responding to visual stimuli from either side, apparently recognized his wife's voice, and spoke a few words. Cytology of the CSF at the time of the shunt demonstrated suspicious cells. Several weeks after the shunt procedure, the patient again lapsed into coma and died approximately four months after admission to the hospital.

PATHOLOGICAL FINDINGS Postmortem examination revealed the presence of a firm tumour arising from the left upper lobe bronchus, approximately 8 cm in diameter. Both lungs were congested and bilateral bronchopneumonia was present. No metastases were observed in the lungs but multiple metastatic lesions were found in the liver, both adrenal glands, and lymph nodes of the thorax and abdomen. An old, healed myocardial infarct was noted and there was moderate generalized arteriosclerosis. Microscopic examination of the primary lung tumour and the metastases revealed an undifferentiated small cell carcinoma.

Gross external examination of the brain revealed the gyral pattern to be of normal configuration. A polyethylene shunt was in place at the posterior extent of the right superior frontal gyrus. The vessels at the base of the brain were thin, delicate, widely patent with no evidence of significant atherosclerosis. There was no evidence of uncus or cerebellar herniation.

After fixation by immersion in 10% buffered formalin, the brain was examined by serial coronal sections at 1 cm intervals. A patent intraventricular shunt was in place passing through the foramen of Monro into the third ventricle. The caudal aspect of the third ventricle was filled with grey-white, granular, friable tissue which was contiguous with a large midline mass invading the medial aspect of the thalamus bilaterally and extending along the Sylvian aqueduct into the dorsal midbrain to the level of the rostral pons. In its greatest extent, the mass measured approximately 3.0 cm medially by 3.5 cm dorsoventrally by 3.5 cm rostrocaudally. The lesion had slightly more mass on the right side with slight displacement of the third ventricle to the left. Small, well-demarcated foci of tan-grey granular tumour were observed in the following locations: (1) at the lateral ventricular angle on the left involving the superior aspect of the head of the caudate nucleus; (2) the septum pellucidum at the level of the anterior commissure; (3) the floor of the left temporal horn 5 mm lateral to but not involving Ammon's horn; (4) the left occipital lobe. These lesions resided in tissue adjacent to the ventricular system with ulceration of the overlying ependymal surfaces. Gross

FIG. 3 Section through the mammillary bodies demonstrating the absence of pathological changes in this region. Luxol-fast blue PAS stain, $\times 5$.

examination and extensive microscopic sectioning of the mammillary bodies, mammillothalamic tracts, and anterior thalamus found them to be free of metastatic involvement, and without significant oedema or reactive changes. Ammon's horn configuration was examined bilaterally and revealed no histological alteration. Microscopical examination of the thalamus demonstrated extensive tumour invasion of the medial thalamus bilaterally. Although accurate topo-

graphical localization was difficult, the dorsomedial nuclei were largely destroyed by tumour. Other involved structures included the centromedian, medial pulvinar, and habenular nuclei and the stria medullaris. In the brain-stem, tumour tissue was confined to the dorsal aspect distributing in a ring-like fashion around the aqueduct, replacing periaqueductal structures in a radius of approximately 6 mm. The histological appearance of the tumour tissue of the brain was similar to that found in the lung and other viscera.

DISCUSSION

This case represents an instance of the occurrence of amnesia associated with bilateral tumour invasion of the medial and posterior thalamus, including medial dorsal nuclei, without concomitant involvement of the mammillary bodies or anterior thalamus. This, of course, does not prove that the medial dorsal or other thalamic nucleus is the critical anatomical substratum for memory disorder in diencephalic disease, nor does it imply that the mammillary bodies are not important in memory function. Our observations do, however, support the contention of Victor *et al.* (1971) that pathology involving the medial dorsal thalamic nuclei can be associated with amnesia without concurrent disease of the mammillary bodies. Admittedly, brain tumours produce much of their symptomatology secondary to surrounding oedema and it may be argued that this situation is not comparable with the more discrete lesions seen in the classical Wernicke-Korsakoff syndrome. However, the mammillary bodies, in this case, were reasonably separated from the tumour mass and were free of oedema when examined by conventional methods. Likewise, the small implants in the septum, left caudate nucleus, and left inferior temporal and occipital lobes, all adjoining the ventricular system, can reasonably be considered to be late distant seeding from the original tumour site and not important in the pathogenesis of the amnesia, which was a presenting symptom.

Case 1 of Sprockin and Sciarra (1952) also demonstrated tumour invasion of the thalami with sparing of the mammillary bodies. However, a more specific description of the thalamic pathology was lacking and these authors pro-

posed that it was merely the deep midline location of the tumours which was responsible for the occurrence of Korsakoff's psychosis in their patients.

Delay *et al.* (1964) reviewed a large number of reports concerning memory disorder in patients with intracranial tumour. They cited 56 cases in addition to their three, in which they found the features of 'Korsakoff's psychosis' convincing. Twenty-one craniopharyngiomas, two pituitary adenomas, and nine tumours of other cell type invading the floor of the third ventricle were included. In only 13 was there associated ventricular dilatation. This latter observation would seem to detract from the possibility that increased intracranial pressure was a major factor in the production of memory dysfunction in those cases. Busch (1940) and Williams and Pennybacker (1954) also considered but discounted the importance of intracranial hypertension in cases of tumour in the region of the third ventricle to account for impairment of memory. Kahn and Crosby (1972) reported five cases of craniopharyngioma which impinged on the third ventricular floor. Three of their patients demonstrated Korsakoff-like psychosis preoperatively and in each this cleared after successful surgery. The other two developed amnesia only after operation; in one this eventually cleared while the other died during the period of memory disturbance. This report emphatically implicated the mammillary bodies as the impaired structures underlying the occurrence of amnesia in their cases. They carried the hypothesis further by proposing interruption of a circuit connecting limbic structures like that proposed by Papez (1937) to account for similar memory disorders reported with lesions of anatomically separated parts of the circuit. Hartley *et al.* (1974) likewise thought that the Korsakoff syndrome in their patient with a pituitary adenoma was related to interruption of Papez's circuit in the hypothalamus. This same patient presented with intermittent episodes of transient global amnesia which prompted the authors to point out the similarity of the two amnesic syndromes. Delay *et al.* (1964) emphasized the importance of a simpler circuit underlying memory function, linking the hippocampal formation with the mammillary bodies and anterior thalamus *via* the fornices and mammillothalamic tracts.

Interestingly, there was a striking paucity of involvement of the anterior thalamus in their cited cases but no apparent effort was made to correlate memory loss with other parts of the thalamus.

It seems evident that, in a number of the reviewed cases of tumours affecting the diencephalon, the lesion was relatively confined to the floor of the third ventricle, thus strongly suggesting that one or more structures in this region are indeed important in subserving memory function. It appears, therefore, that the thalamus in the region of the medial dorsal nucleus is not consistently involved in patients with tumours occurring in association with amnesia as observed in those with Korsakoff's psychosis developing on a background of nutritional depletion (Victor *et al.*, 1971).

Any unitary anatomical hypothesis which includes both mammillary bodies and medial dorsal thalamic nucleus as important in memory function, presents a conflict on the basis of existing anatomical knowledge. Apparently, there is no single structure or known inter-related group of structures which act as the mandatory substratum for amnesia occurring with lesions of the mesodiencephalic region. Rather, it appears that small lesions in a number of different sites, the anatomical relationship of which is not yet entirely clear, can produce a remarkably similar and profound memory disturbance. Such sites include the fibre tracts, an area yet to be carefully studied in cases of amnesia, which course through the diencephalon and distribute widely throughout the brain. However, lesions placed in these tracts have been shown to eliminate learned behaviour in experimental animals (Kent and Grossman, 1973). Since a large portion of these nerve fibres originate in the brain-stem, certain brain-stem centres might be assigned a more specific relationship to memory and learning than heretofore. In this regard, small bilateral mid-pontine lesions, in the floor of the fourth ventricle, including destruction of the locus coeruleus, were found to be associated with impaired learning ability of reward induced behaviour in rats (Anlezark *et al.*, 1973). These fibre systems may prove to be a fruitful area for study in future investigations of the anatomy of amnesia.

REFERENCES

- Anlezark, G. M., Crow, R. J., and Greenway, A. P. (1973). Impaired learning and cortical norepinephrine after bilateral locus coeruleus lesions. *Science*, **181**, 682–684.
- Busch, E. (1940). Psychical symptoms in neurosurgical disease. *Acta Psychiatrica Scandinavica*, **15**, 257–290.
- Delay, J., and Brion, S. (1958). Syndrome de Korsakoff et corpus mamillaires. *Encéphale*, **47**, 99–142.
- Delay, J., Brion, S., and Derouesne, C. (1964). Syndrome de Korsakoff et étiologie tumorale. *Revue Neurologique*, **111**, 97–133.
- Gamper, E. (1928). Zur Frage der Polioencephalitis haemorrhagica der chronischen Alkoholiker: Anatomische Befund beim Alkoholischen Korsakow und ihre Beziehungen zum Klinischen Bild. *Deutsche Zeitschrift für Nervenheilkunde*, **102**, 122–129.
- Hartley, R. C., Heilman, K. M., and Garcia-Bengochea, F. (1974). A case of a transient global amnesia due to a pituitary tumor. *Neurology (Minneapolis)*, **24**, 998–1000.
- Hécaen, M. H., and de Ajuriaguerra, J. (1956). Les encéphalopathies alcooliques subaiguës et chroniques. *Revue Neurologique*, **94**, 528–555.
- Kahn, E., and Crosby, E. C. (1972). Korsakoff's syndrome associated with surgical lesions involving the mammillary bodies. *Neurology (Minneapolis)*, **22**, 117–125.
- Kent, E. W., and Grossman, S. P. (1973). Elimination of learned behaviors after transection of fibers crossing the lateral border of the hypothalamus. *Physiology and Behavior*, **10**, 953–963.
- Malamud, N., and Skillicorn, S. A. (1956). Relationship between the Wernicke and the Korsakoff syndrome. *Archives of Neurology and Psychiatry*, **76**, 585–596.
- Papez, J. W. (1937). A proposed mechanism of emotion. *Archives of Neurology and Psychiatry*, **38**, 725–743.
- Sprockin, B. E., and Sciarra, D. (1952). Korsakoff's psychosis associated with cerebral tumours. *Neurology (Minneapolis)*, **2**, 427–434.
- Victor, M., Adams, R. D., and Collins, G. H. (1971). *The Wernicke-Korsakoff Syndrome*. Davis: Philadelphia.
- Williams, M., and Pennybacker, J. (1954). Memory disturbances in third ventricle tumours. *Journal of Neurology, Neurosurgery, and Psychiatry*, **17**, 115–123.