A dominant form of adult neuronal ceroid-lipofuscinosis (Kufs' disease) with an associated occipital astrocytoma: early diagnosis by cortical biopsy

ROBERT A. BRODNER,¹ JAE M. NOH, AND EDWARD J. FINE

From the Department of Neurosurgery, The Mount Sinai School of Medicine of the City University of New York, New York, N.Y., and Veterans Administration Hospital, Bronx, New York, and Department of Neurology, Veterans Administration Hospital, Lyons, New Jersey, U.S.A.

SYNOPSIS A patient with a dominantly inherited form of Kufs' disease and an associated occipital astrocytoma is presented. This is the first reported case in which the diagnosis of Kufs' disease was made by a cortical biopsy several years before its expected clinical onset. The nosology of this disease, and its clinical, genetic, and histopathological characteristics are discussed. The establishment of an early diagnosis by cortical biopsy and its implications are considered

Kufs' disease, an adult form of neuronal ceroid-lipofuscinosis, is a very rare and fatal disease (DeVries, 1968; Kornfeld, 1973). Most commonly, the various types of neuronal ceroid-lipofuscinoses are inherited as Mendelian recessives (Seitelberger *et al.*, 1967; Boehme *et al.*, 1971). This report concerns a patient with an occipital astrocytoma and a documented family history of an autosomal dominantly inherited type of Kufs' disease, who was definitely diagnosed as having this disease by a cortical biopsy taken at the time of a craniotomy some seven years before the expected onset of prominent symptomatology. A definitive diagnosis of Kufs' disease so long before its expected onset has not been established previously, nor has association of a cerebral neoplasm with Kufs' disease been reported.

CASE HISTORY

The patient is a 24 year old right-handed white male of German-Irish extraction who was first admitted to the Veterans Administration Hospital, East Orange, New Jersey, on 24 September 1973 with a 2½ year

history of intermittent episodes of 'flashing bright lights' in his right temporal visual field. These were followed by a 15 to 20 minute period of loss of consciousness. The patient had experienced approximately 30 such episodes which increased in frequency

FIG. 1 Left carotid angiogram, lateral view. An area of discrete calcification is noted in the occipital region. The adjacent cortical veins are bowed and stretched.

¹ Requests for reprints: Dr R. Brodner, Department of Neurosurgery, The Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, N.Y. 10029, U.S.A.

(Accepted 15 October 1975.)

during the six months before admission. He received 100 mg diphenylhydantoin three times daily for five months before admission. At the time of hospitalization, the patient was working effectively and without difficulty as a computer programmer.

FAMILY HISTORY The patient is a member of a family with a well-documented history of an autosomal dominantly inherited form of Kufs' disease. The condition always becomes manifest around age 31 years, and usually presents as a cerebellar syndrome. Other consistent and prominent findings are generalized seizures, progressive dementia, myoclonias, and moderate systolic and diastolic hypertension. The disease is ultimately fatal with an average duration from time of onset of seven years.

EXAMINATION The patient presented as a well-developed, well-nourished, 24 year old white male, attentive, cooperative, and in no physical distress. His blood pressure of 130/80 mmHg recorded in both upper extremities was not altered by position. Except for a 1 × 2 cm lipoma, present in the right axillary region, the physical examination was unremarkable.

The neurological examination was entirely within normal limits. The neuro-ophthalmology consultant described normal visual fields and fundi. The haemo-

gram, serum electrolytes, urea nitrogen determinations, and urinalysis were normal. Cerebrospinal fluid analysis was normal.

Radiographs of the chest showed no abnormality. Skull radiographs demonstrated an irregular calcification in the left occipital region. Electroencephalography revealed left posterior quadrant slowing, and left mid-temporal paroxysmal activity. Brain scan performed on 27 September, defined a small, well-circumscribed left occipital lobe lesion. Brain imaging two weeks later showed that the left occipital lesion had increased in size. On 5 October 1973, selective left carotid and left vertebral transfemoral angiography demonstrated a finely calcified avascular mass within the left occipital lobe (Fig. 1). The Weschler Adult Intelligence scales were a verbal IQ of 97 and a performance IQ of 104. No disturbances of affect or thought were revealed. A rectal biopsy was performed and reported as normal.

On 3 October 1973, the patient was observed to be unconscious for 10 minutes and on awakening complained of having seen a 'flashing light' in his right eye, and suffered from an occipital headache, which persisted for five hours. The patient was receiving 100 mg diphenylhydantoin three times daily by mouth at this time.

OPERATION After transfer to the Veterans Adminis-

FIG. 2 (a) Photomicrograph of occipital cortex showing depletion of neurons, brain biopsy. H and E, × 180. (b) Photomicrograph demonstrating intracytoplasmic PAS positive staining lipofuscin granules, brain biopsy. PAS-LFB, × 400.

tration Hospital, Bronx, New York, the patient consented to a craniotomy on condition that an effort be made to discover if he had the same disease as his mother had. He was engaged to be married and desired to inform his fiancée of his state of health. At craniotomy a cystic tumour was found in the left occipital lobe on 25 October 1973. Drainage of the cyst, total removal of the tumour, and a biopsy of occipital cortex were accomplished.

PATHOLOGICAL EXAMINATION *Light microscopy* A $0.5 \times 0.5 \times 0.5$ cm portion of occipital tissue adjacent to the tumour was embedded in paraffin and sectioned serially. The 5 mm thick sections were stained by haematoxylin-eosin (H and E), Bodian, Luxol Fast Blue-PAS methods. Several perikarya in each section contained clumps of pale yellow-brown intracytoplasmic granules which produced rarified areas in the H and E stained cytoplasm and stained positive with PAS. The perikarya appeared to be slightly more reduced in number than would be expected in a patient of this age (Fig. 2). The myelin was well preserved. No neurofibrillary tangles were noted in the Bodian stained sections.

The $1.7 \times 1.0 \times 0.7$ cm light-tan portion of tumour contained many areas of calcification. H and E stained sections revealed many aggregates of deeply basophilic round to oval lamellated calcospherites. The tumour cells had small round to oval uniformly

dark basophilic nuclei. These cells had elongated processes and resembled fibrillary astrocytes. Multiple areas of microcystic degeneration were present (Fig. 3).

Electron microscopy Appropriately sized samples of occipital cortex and tumour were fixed in 4% glutaraldehyde and post-stained with 1% osmic acid buffered with 0.1 molar cacodylate. The tissue was embedded in Epon and sectioned in an ultramicrotome.

The neuronal perikarya of the occipital cortex contained irregular electron dense bodies which corresponded to the lipofuscin granules observed by light microscopy. Occasionally these bodies were adjacent to or surrounded by electron lucent vacuoles (Fig. 4). No beaded membranes or fingerprint-like patterns were noted.

Electron microscopy of the tumour revealed slightly elongated nuclei with moderately dense chromatin. The cytoplasm, which was distributed into bipolar processes, contained endoplasmic reticulum, mitochondria, and round electron dense bodies resembling lysosomes. The unique feature of these cells was the presence of intracytoplasmic fibres which were frequently arranged in parallel bands. The electron microscopic appearance of these cells resembled closely that of fibrillary astrocytes (Fig. 5). The diagnosis made was (1) left occipital cystic grade I

FIG. 3 (a) Photomicrograph revealing dark staining lamellated calcospherites, microcysts, and elongated tumour cells. H and E, $\times 170$. (b) Photomicrograph demonstrating elongated tumour cell nuclei and microcystic areas. H and E, $\times 600$.

FIG. 4 (a) *Electron micrograph illustrating cytoplasmic electron dense bodies and vacuoles, resembling lipofuscin granules. Brain biopsy. $\times 7\,990$.* (b) *Electron micrograph showing irregular cytoplasmic electron dense bodies which occasionally surround vacuoles. Brain biopsy $\times 14\,060$.*

FIG. 5 *Electron micrograph demonstrating lysosomal-like bodies, nucleus, and intracytoplasmic fibres. Tumour cells. $\times 14\,000$.*

astrocytoma with calcification, and (2) neuronal ceroid-lipofuscinosis, consistent with a clinical diagnosis of Kufs' Disease.

The patient's postoperative course was unremarkable. He displayed a right inferior homonymous quadrantanopsia after surgery. Three weeks after operation he was discharged on 100 mg diphenylhydantoin three times daily.

The patient was readmitted to the East Orange Veterans Administration Hospital on 7 January 1974, for further evaluation. The blood pressure was 120/70 mmHg. The pertinent physical findings included a well-healed left occipital craniotomy scar, right inferior congruous quadrantanopsia, mild bilateral papilloedema, and an abnormal mental status. The patient had a 'flat' affect, and slight difficulty with recall and abstract reasoning.

Electron and light microscopic examination of a percutaneous liver biopsy specimen was interpreted as normal.

He was discharged on 17 January 1974, after 30 mg phenobarbitone three times daily was added to his anticonvulsant regimen.

During July and August 1974, the patient's visual

fields, EEG, and mental status were re-examined. Campimetry demonstrated right homonymous congruous hemianopsia most dense in the inferior visual fields with macular sparing. An EEG was performed, and comparison of this EEG with that obtained in November 1973 indicated that the 1974 recording contained less slow activity.

The patient scored a Verbal IQ of 92 and a Performance IQ of 104 on the Wechsler Adult Intelligence scale. Although these overall scores did not differ significantly from the 1973 results, there was a decline into the defective range in visual motor tasks, performance, abstract reasoning, and picture arrangement.

The patient was admitted to Veterans Administration Hospital, Lyons, New Jersey in May 1975. The awake EEG contained no focal slow wave activity. The patient showed further deterioration in visual motor performance, the most noteworthy change being his inability to recite the last five letters of the alphabet. He claimed that his short-term memory loss prevented him from properly programming a computer.

Electroencephalography and isotope brain scan performed during September 1975 were interpreted

as normal. The neurological examination was identical with that obtained in 1974.

DISCUSSION

The nosology of the neuronal ceroid-lipofuscinoses is unclear since their aetiology and pathogenesis are unknown. Zeman and Dyken (1969) classified the collection of heterogeneous clinical entities referred to as 'amaurotic familial idiocy' into two distinct groups: the gangliosidoses and the neuronal ceroid-lipofuscinoses. The gangliosidoses are characterized by inborn deficiencies of lysosomal enzymes resulting in intraneuronal accumulation of GM1 and GM2 gangliosides. Among the GM2 gangliosidoses, Tay-Sachs disease is most frequent (Zeman and Dyken, 1969; Boehme *et al.*, 1971).

The neuronal ceroid-lipofuscinoses demonstrate no altered ganglioside metabolism but rather intraneuronal accumulation of ceroid and lipofuscin (Zeman and Dyken, 1969; Boehme *et al.*, 1971; Kornfeld, 1973). The biochemical pathogenesis remains unknown (Pallis *et al.*, 1967; Zeman and Dyken, 1969; Boehme *et al.*, 1971). Thin layer chromatography has shown normal phospholipid and ganglioside patterns (Pallis *et al.*, 1967; Zeman and Dyken, 1969). The diagnosis is based on demonstration of excessive intraneuronal, astrocytic, and visceral accumulation of autofluorescent granules which ultrastructurally and histochemically have been defined as ceroid and/or lipofuscin (Kufs, 1929; Wallace *et al.*, 1966; Boehme *et al.*, 1971; Chou and Thompson, 1970; Coggi, 1972). Lipopigment accumulation is accompanied by distension and ballooning of the neuronal perikarya. The diffuse loss of neurones produces gross brain atrophy (Winkelman, 1947; Fine *et al.*, 1960; Pallis *et al.*, 1967; Zeman and Dyken, 1969).

Neuronal ceroid-lipofuscinosis can be divided into various subtypes based upon phenotypical criteria. Boehme *et al.* (1971) described several such types, including the Kufs' type, which has been erroneously misnamed 'adult familial amaurotic idiocy'.

The clinical picture of Kufs' disease is not well defined because of the variability of its clinical course and symptoms (Kufs, 1929; Winkelman, 1947; Boehme *et al.*, 1971). The variability in location of the histopathological process results

in an inconstant clinical syndrome (Winkelman, 1947; Fine *et al.*, 1960). The most common symptoms are dementia, cerebellar ataxia, involuntary movements, rigidity, myoclonus and seizure disorders (Kufs, 1929; Zeman and Dyken, 1969; Boehme *et al.*, 1971). Visual symptoms are usually not present (Kufs, 1931). Nearly all of the reported cases of Kufs' disease have shown an autosomal recessive inheritance (Kufs, 1931; Boehme *et al.*, 1971).

The patient reported here is a member of a family with a dominantly inherited form of Kufs' disease documented by clinical, genetic, and pathomorphological criteria (Boehme *et al.*, 1971). The patient's mother was severely symptomatic and totally incapacitated by complete incoordination, inability to speak, and massive myoclonus. Boehme *et al.* (1971) studied this family extensively and reported striking uniformity in the time of onset and the clinical manifestations among the affected siblings. Grand mal seizures, progressive cerebellar ataxia, myoclonic jerks and massive myoclonias, progressive dementia, and essential hypertension are the clinical features of the disease. Its onset is uniformly at the age of 31 years. In this case, the opportunity for cortical biopsy at craniotomy enabled a definitive diagnosis of Kufs' disease to be established at age 24 years, seven years before the expected appearance of distinctive signs and symptoms.

Azurophilic hypergranulation of polymorphonuclear neutrophils, although not pathognomonic for the neuronal ceroid-lipofuscinoses and Kufs' disease, was found in all the living patients of this family and was absent in ascertained non-carriers (Boehme *et al.*, 1971). Three healthy children, including our patient, of those affected family members demonstrated an increased although mild, azurophilic hypergranulation and no lymphocytic vacuolization (Boehme *et al.*, 1971). Zeman and Dyken (1969) note that, whenever it is present in an affected patient, azurophilic hypergranulation of the neutrophils is seen in the parents and in two-thirds of the siblings of the patients, suggesting that this leucocytic abnormality may act as a marker for the mutated gene in these families. These observations in the peripheral leucocytes, however, should be interpreted with the greatest caution, since their presence is inconstant and their mild

appearance may represent nothing more than a variant of the normal granulation.

Histologically, the most prominent pathological finding in Kufs' disease is severe neuronal loss, the sites of maximal involvement being the cerebral cortex, cerebellum, substantia nigra, and various other subcortical nuclei (Kufs, 1929; Zeman and Dyken, 1969; Kornfeld, 1973). The remaining neuronal perikarya are enlarged by an accumulation of abnormally large amounts of yellow-brown cytoplasmic granules, which have the appearances of a ceroid-lipofuscin type of pigment (Kufs, 1929; Pallis *et al.*, 1967; Boehme *et al.*, 1971). These distended, ballooned neurones are seen ubiquitously in virtually all parts of the central nervous system. Neurones of the substantia nigra contain coarse spheroid inclusions termed 'myoclonus bodies of the protein type' as defined by Seitelberger (Seitelberger, 1962; Seitelberger *et al.*, 1967).

Electron microscopy reveals, most frequently, intraneuronal lipopigment granules with a variegated internal structure composed of granular matter, and membranes containing a wide variety of multilamellar and fingerprint-like patterns (Pallis *et al.*, 1967; Chou and Thompson, 1970). Kornfeld's (1973) ultrastructural examination of tissue from a patient with Kufs' disease revealed lipofuscin as the main substrate of swelling in the distended neurones. In the postmortem electron microscopic studies performed by Boehme *et al.* (1971) upon our patient's uncle, the multilamellar and fingerprint patterns and lattices, which describe the internal structure of lipopigment bodies in the tissues of other patients with ceroid-lipofuscinosis, were not found. The ultrastructure of intraneuronal lipopigment is variable, and therefore, of limited diagnostic value.

Since the accumulation of lipofuscin in the cytoplasm of some neurones is a normal concomitant of the aging process, the significance of diffuse lipofuscinosis is difficult to define. The question arises whether lipofuscin pigments accumulate simply as a function of age or in response to a variety of injurious conditions. Pallis *et al.* (1967) state that the occurrence of lipofuscin in the neurones of younger subjects implies abnormal lipid metabolism, and that the presence of lipofuscin in all neurones with

ballooning due to its accumulation is considered abnormal at any age.

The pathogenesis of neuronal ceroid-lipofuscinosis remains obscure. It is apparent that different mutant genes are involved in the production of neuronal ceroid-lipofuscinosis as exemplified by some cases possessing a recessive pattern of inheritance and others demonstrating dominant inheritance, as in this reported case. This is further suggested by the variability noted in phenotypes. The involvement of different mutant genes in the production of neuronal ceroid-lipofuscinosis necessitates criteria other than phenotypical to be established before precise diagnostic characterization of this group of disorders can be achieved.

In this patient, a cortical biopsy done at the time of occipital craniotomy for tumour removal allowed a definite diagnosis of Kufs' disease to be established several years before its expected clinical onset. This is the first reported case which demonstrates that the histopathological changes indicative of Kufs' disease occur before its clinical presentation, and that early diagnosis is possible. It may be suggested that, if a family history of Kufs' disease be present, a cortical biopsy can be performed on a suspected patient for diagnostic purposes as well as for genetic consultation.

The authors gratefully acknowledge the assistance of Miss Lyn Stipp and Dr D. Boehme in the preparation of the electron micrographs.

REFERENCES

- Boehme, D. H., Cottrell, J. C., Leonberg, S. C., and Zeman, W. (1971) A dominant form of neuronal ceroid-lipofuscinosis. *Brain*, **94**, 745-760.
- Chou, S. M., and Thompson, H. G. (1970). Electron microscopy of storage cytosomes in Kufs' disease. *Archives of Neurology (Chic.)* **23**, 489-501.
- Coggi, G. (1972). Late life neuronal lipidosis (Kufs' disease). Case 8. *Missouri Medicine*, **69**, 21-23.
- DeVries, E. (1968). A case of the adult form of amaurotic idiocy, diagnosed during life as Huntington's chorea. *Psychiatry, Neurologia, Neurochirurgia*, **71**, 203-209.
- Fine, D. I. M., Barron, K. D., and Hirano, A. (1960). Central nervous system lipidosis in an adult with atrophy of the cerebellar granular layer. A case report. *Journal of Neuropathology and Experimental Neurology*, **19**, 355-369.
- Kornfeld, M. (1973). Generalized lipofuscinosis (generalized Kufs' disease). *Journal of Neuropathology and Experimental Neurology*, **31**, 668-682.
- Kufs, H. (1929). Über einen Fall von Spätform der amaurotischen Idiotie mit atypischem Verlauf und mit terminalen schweren Störungen des Fettstoffwechsels im Gesamtorg-

- ganismus. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **122**, 395–415.
- Kufs, H. (1931). Über einen Fall von spätester Form der amaurotischen Idiotie mit dem Beginn im 42. und Tod im 59. Lebensjahre in klinischer, histologischer und vererbungs-pathologischer Beziehung. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **137**, 432–448.
- Pallis, C. A., Duckett, S., and Pearse, A. G. E. (1967). Diffuse lipofuscinosis of the central nervous system. *Neurology (Minneapolis)*, **17**, 381–394.
- Seitelberger, F. (1962). Sonderformen zerebraler lipoidosen. In *Proceedings of the IV International Congress of Neuropathology*, pp. 3–13. Edited by H. Jakob. Thieme: Stuttgart.
- Seitelberger, F., Jakob, H., and Schnabel, R. (1967). The myoclonic variant of cerebral lipidosis. In *Inborn Disorders of Sphingolipid Metabolism*, pp. 43–74. Edited by S. M. Aronson and B. W. Volk. Pergamon: New York.
- Wallace, B. J., Volk, B. W., Schneck, L., and Kaplan, H. (1966). Fine structural localization of two hydrolytic enzymes in the cerebellum of children with lipidoses. *Journal of Neuropathology and Experimental Neurology*, **25**, 76–96.
- Winkelman, N. W. (1947). The adult form of amaurotic idiocy. A clinicopathological report of two cases. *Transactions of the American Neurological Association*, **72**, 123–125.
- Zeman, W., and Dyken, P. (1969). Neuronal ceroid-lipofuscinosis (Batten's disease): relationship to amaurotic family idiocy? *Pediatrics*, **44**, 570–583.