Progressive myoclonic epilepsy due to Gaucher's disease in an adult

J. O. KING

From the National Hospital for Nervous Diseases, Queen Square, London

SYNOPSIS A 39 year old Jewish male with a 22 year history of progressive myoclonic epilepsy was found to have Gaucher cells in his sternal bone marrow. The diagnosis of Gaucher's disease was confirmed by the demonstration of beta-glucosidase deficiency in fibroblasts. Although neurological involvement is extremely rare in adults with Gaucher's disease, this disease is another lipidosis which should be considered in patients with progressive myoclonic epilepsy.

By progressive myoclonic epilepsy is meant the striking combination of grand mal seizures and generalized myoclonus which, in some instances, may be associated with intellectual deterioration. A mild degree of myoclonic jerking is common in epileptics, particularly before a seizure (Hodskins and Yakovlev, 1930), but in myoclonic epilepsy it may be prominent, continuous, and disabling. Recording of cerebral evoked potentials (Halliday, 1967) is a useful confirmatory investigation, as in myoclonic epilepsy the responses are usually grossly enlarged. The clinical entity was originally reported by Unverricht (1891, 1895) and later by Lundborg (1903, 1913) whose work pointed to an autosomal recessive pattern of inheritance. Lafora and Glueck (1911) described the amyloid cytoplasmic inclusion bodies throughout the nervous system, but later reports suggested that at least three different underlying clinical and pathological groups were present and these have been reviewed by Halliday (1966).

Lafora body disease is characterized by onset in the second decade with rapidly progressive intellectual deterioration, incessant myoclonus, grand mal seizures, and death within 10 years. Parental consanguinity is common. Harriman and Miller (1955) demonstrated that the inclusion bodies, which contain mucopolysaccharide, are also present in the liver and heart. An identical clinical picture of progressive myoclonic epilepsy without Lafora bodies has been reported (Matthews et al., 1969).

In a second group, some patients with myoclonic epilepsy have had cerebellar ataxia or extrapyramidal signs suggesting involvement of the olivodentate system by primary degenerative diseases. Dysynergia cerebellaris myoclonica (Hunt, 1921) is included in this category as well as patients with Friedreich's ataxia who develop myoclonus and epilepsy. The onset occurs from the second decade onwards and runs a more benign course with less involvement of higher cerebral functions.

The third group of patients have an underlying lipidosis which is almost invariably juvenile amaurotic familial idiocy. The non-infantile types of amaurotic familial idiocy have become known by the term neuronal ceroid lipofuscinosis (Zeman, 1974) since the identification of the stored neuronal pigments. Sjögren (1931) clearly distinguished between infantile amaurotic familial idiocy (Tay-Sachs disease) and the juvenile form. In the latter he recognized the characteristic syndrome of epilepsy beginning between 6 and 12 years of age, with progressive extrapyramidal rigidity. Although most patients with juvenile amaurotic familial idiocy have fits, in a few instances the degree of associated myoclonus has suggested progressive myoclonic epilepsy. Marinesco (1925) reported a case of progressive myoclonic epilepsy in a boy aged 6 years with amaurotic familial idiocy in whom the brain showed lipid deposits in many ganglion cells.
with the additional feature of small rounded well-defined bodies, similar to the nucleus, in the cytoplasm. Similar cases have been described by Liebers (1927), Haddenbrock (1950), Marchand et al. (1956), de Vries and Amir (1964), and Klinken-Rasmussen and Dygge (1965). Diezel (1957), reinvestigating Haddenbrock’s case and reporting another, demonstrated that the small round bodies consisted predominantly of protein with small amounts of glycolipid.

Seitelberger et al. (1967) defined this ‘myoclonic variant of amaurotic familial idiocy’ when he reported eight patients, aged between 2 and 10 years who presented with grand mal fits and cerebellar ataxia followed by psychomotor deterioration, myoclonus, blindness with optic atrophy and retinitis pigmentosa, and who finally died of dementia and cachexia. They showed generalized neuronal lipid storage, with protein type inclusion bodies in the cells of the thalamus, subthalamic nucleus, substantia nigra, dentate nucleus, inferior olive, and locus caeruleus. It should be noted that these bodies are quite different from Lafora bodies, which consist of mucopolysaccharide in the form of polyglucosans (Yokoi et al., 1968).

Two patients with progressive myoclonic epilepsy due to an underlying lipidosis do not fall into the type described by Seitelberger et al. (1967). One, with features of amaurotic familial idiocy—namely, cherry red spots in the fundi, optic atrophy, and a family history of blindness and death in infancy—also had cystic changes in radiographs of long bones, pathological fractures, and storage cells in the sternal bone marrow which morphologically resembled Gaucher cells. This patient developed generalized myoclonus from the age of 10 years, grand mal seizures at 23 years, and finally died at 31 years of age with minimal evidence of dementia (Glasgow, 1957; Halliday, 1967). The patient reported by Pallis et al. (1967) presented in the sixth decade with progressive cerebellar ataxia, intellectual deterioration, myoclonus and grand mal seizures and was clinically diagnosed as dyssynergia cerebellaris myoclonica. Neurones throughout the nervous system were heavily pigmented with lipofuscin and the authors suggested that diffuse lipofuscinosis should be considered as another form of lipidosis.

The following case report is of a 39 year old man with a 22 year history of progressive myoclonic epilepsy who was found to have histological and biochemical evidence of Gaucher’s disease.

CASE REPORT

M.S. (NHQS A406) This 39 year old single clerk was admitted to the National Hospital in August 1973 for investigation of intractable grand mal seizures and myoclonus.

He was born in South Africa of Jewish parents who originated from Lithuania and who were first cousins. There are two other unaffected siblings and no known family history of epilepsy or of anaemia. The patient himself was well until 17 years of age when he had a sudden episode of dizziness followed by brief loss of consciousness and generalized clonic movements of his limbs. Thereafter, he continued to have seizures at monthly intervals and in addition developed shock-like jerking of his right arm, particularly before seizures and in the early morning.

At the time when the illness started he was studying part-time for a degree in commerce which he passed in 1956; however, in 1960 he failed to pass his final chartered accountancy examinations. In 1961 he came to England as a senior assistant in a firm of accountants. In that year he was first seen at the National Hospital and no abnormalities were noted on examination and routine blood examination; serology and skull radiographs were normal. He had had a normal pneumoencephalogram and carotid angiogram in 1957 in South Africa. His electroencephalogram was grossly abnormal with very frequent paroxysms of generalized irregular multiple spikes and waves. A diagnosis of idio-pathic epilepsy was made and he was discharged on anti-convulsants.

His epilepsy remained reasonably well controlled until 1966 when, after an influenza-like illness, both the seizures and myoclonic jerking increased in frequency. When next seen in 1968 he had been reduced to working as a ledger checker. Examination revealed slow deliberate speech broken up by jerks, typical brief irregular shock-like movements of his face and upper limbs with mild incoordination. His performance IQ was 77 and verbal IQ 105 (WAIS) which was felt to indicate definite evidence of intellectual impairment, although subsequent psychometry has shown no further change. Cerebral evoked responses to electrical stimulation of either hand produced grossly enlarged potentials with early surface positive components of between 16 and 19 μV from the

9 This patient was presented at the meeting of the Royal Society of Medicine held at the National Hospital on 5 December 1974.
Progressive myoclonic epilepsy due to Gaucher's disease in an adult

right hemisphere and 11 to 13 μV from the left hemisphere (Fig. 1). It was felt at this stage that the patient had progressive myoclonic epilepsy.

In the next four years he had further admissions for adjustments to his anticonvulsant therapy but, despite trials of numerous drugs, his seizures continued to occur about once weekly.

In 1973 his fits were entirely nocturnal and were accompanied by urinary incontinence. Those observed in hospital were of sudden onset with rigidity of all four limbs and body followed by a clonic phase lasting several minutes. His major disability was his myoclonic jerks which prevented him from writing and caused him to take an hour over dressing. His treatment consisted of primidone, phenytoin sodium, sulphamide, nitrazepam, diazepam, and methylphenidate.

He had slow slurred speech with a mild nominal dysphasia. His gait was normal, but for very marked myoclonic jerking which involved his face, arms, and legs. The myoclonus was increased by voluntary movement such as drinking from a cup or attempting to adjust his spectacles, by sudden noises, lights, tactile stimuli, and when his eyes were closed. His visual acuity, fields, and foni were normal but saccadic eye movements were slow in all directions (this will be reported separately). Muscle tone, power, reflexes, and sensation were normal but he had finger-nose and heel-shin ataxia which was thought to be mainly due to his myoclonus. His cardiovascular system, lungs, and abdomen were normal and, in particular, no spleen was palpable.

His electroencephalogram and cerebral evoked responses were unchanged. Other investigations were: haemoglobin 9.4 g/dl, sedimentation rate 7 mm/h, white cell count 2 400 mm−3, (neutrophils 1 440 mm−3, lymphocytes 672 mm−3, monocytes 240 mm−3, eosinophils 24 mm−3), platelets 80 000 mm−3, serum iron 19.9 μmol/l, iron binding capacity 33.6 μmol/l (321 μg/dl), faecal occult blood negative, serum vitamin B12 600 ng/l, serum folic acid 6.0 μg/l, and serum acid phosphatase 20 I.U./l (0–5). Radiological examination of long bones, skull, chest, and pelvis was normal. The sternal marrow was hypocellular with normal erythropoiesis and granulopoiesis but, in addition, large storage cells resembling Gaucher cells were present (Fig. 2). Histochemical examination of the marrow confirmed the numerous foamy cells which morphologically resembled those seen in late onset GMI gangliosidosis or Gaucher's disease. The beta-glucosidase activity of peripheral blood leucocytes was 205 nmol/mg protein/h (100–400) and beta-glucosidase activity of fibroblasts was 35 nmol/mg protein/h (100–500), consistent with Gaucher's disease.

Since discharge the patient has been unable to keep his employment and it has been necessary to admit him to an institution with special facilities for epileptics. The recent introduction of clonazepam has improved the control of his myoclonic jerks and it has been possible to reduce his other anticonvulsants.

Since Brady et al. (1965) demonstrated the deficiency of beta-glucosidase, the enzyme which cleaves glucose from glucosyl ceramide (glucocerebroside), the diagnosis of Gaucher's disease has relied upon evidence of reduced enzyme activity rather than the finding of the typical Gaucher cell. The presence of the latter provides only a tentative diagnosis, as similar cells are found in GMI gangliosidosis where there is a deficiency of beta-galactosidase (Okada and O'Brien, 1968), and in chronic myeloid leukaemia (Kattlove et al., 1969).

In the patient reported here, the storage cells in the bone marrow, the elevated serum acid phosphatase, normal beta-galactosidase, and deficient beta-glucosidase activity point to an unequivocal diagnosis of Gaucher's disease. The absence of a palpable spleen delayed diagnosis and is unusual,
although well recognized (Morgans, 1947; Maloney and Cumings, 1960). The diagnosis of progressive myoclonic epilepsy is justified on the grounds of the extensive myoclonus, and grand mal seizures and the giant cerebral evoked potentials. The degree of intellectual deterioration is difficult to assess because of the effect of the anticonvulsant drugs and also the absence of a formal assessment before the onset of the illness. If present it has been of only a mild degree in 20 years.

If one disregards the neurological features of the present case, the age of onset, prolonged survival, pancytopenia, and Ashkenazi Jewish origin suggest that the patient is suffering from the chronic adult form of Gaucher’s disease. However absence of neurological involvement is the sine qua non for classification in the adult or non-neuronopathic type of Gaucher’s disease as opposed to the infantile form where neurological signs are the rule and death occurs under 2 years of age. There is a further small group known as juvenile or subacute neuronopathic Gaucher’s disease where survival into the second decade is known. Frederickson and Sloan (1972) have reviewed 25 cases, 12 of whom were reported from Sweden by Hillborg (1959). The neurological features of this group were mental retardation, psychotic behaviour disturbances, generalized rigidity, jerky movements, epilepsy, and abnormal electroencephalograms. The jerky movements involved the eyes, mouth, and limbs, but were not described as myoclonic in nature (Herrlin and Hillborg, 1962). The age of onset was in the first six months of life with survival up to 20 years, although six died in the first three years. Of six studied in detail, five patients had a pancytopenia and all had normal radiological examinations before splenectomy.

Despite the absence of neurological signs, by definition, in adult Gaucher’s disease, there have been several case reports of neurological involvement after the first decade (van Bogaert and Fröhlich, 1939; Davison, 1942). Miller et al. (1973) recently reported two siblings, aged 41 and 50 years, with histories of seizures for 12 and 15 years, respectively. Both patients had evidence of intellectual impairment and one had myoclonic jerks before his seizures. Both had supranuclear gaze pareses. The diagnosis of Gaucher’s disease was established in both instances by the presence of Gaucher cells in the spleen and bone marrow and evidence of deficient leucocyte beta-glucosidase activity. Although noting that the neurological features of their patients resembled those seen in juvenile Gaucher’s disease, they concluded that both had adult type Gaucher’s disease. The subject of the present case report appears to have a similar form of Gaucher’s disease and all three cases suggest that, although rare, neurological involvement in adult Gaucher’s disease does occur. Neuropathological evidence of such is necessarily limited. Davison’s case, a 26 year old Polish Jew with adult Gaucher’s disease and facial immobility, had swelling and loss of cells in the putamen and caudate nuclei, slight swelling of Purkinje cells, and large foam cells in the spinal cord when examined histologically. Diezel (1955) has described both perivascular Gaucher cells and ganglion cell changes in the cortex and cerebellum of a 61 year old.

FIG. 2 Sternal bone marrow with a typical Gaucher cell. × 400.
Progressive myoclonic epilepsy due to Gaucher’s disease in an adult

man who apparently had adult Gaucher’s disease. Gaucher cells have been reported in the pituitary and hypothalamus (Teilum, 1944; Morrison and Lane, 1955), spinal cord (Davison, 1942), and meninges (Chang-lo et al., 1967).

Even considering the pattern of involvement of the nervous system in the infantile (Norman et al., 1956) and juvenile forms of Gaucher’s disease (Bird, 1948), there is no evidence of a specific pattern to account for the occurrence of progressive myoclonic epilepsy. The same can be said for the other lipidoses and Lafora body disease where the changes are so diffuse. This contrasts with the frequent finding of dentate and olivary atrophy in cases of the system degeneration type (Meyer, 1963).

Although the long term prognosis for the subject of this case report must be poor, he has already survived more than 20 years since his seizures began. His degree of intellectual impairment is mild and, provided that a drug is found which will control his epilepsy and myoclonus without excessive side-effects, it is conceivable that he could return to some form of useful employment. The advent of clonazepam has provided some hope in this direction and early reports of its use in progressive myoclonic epilepsy are favourable (Laitinen and Toivakka, 1973).

In the clinical context of a patient with persistent myoclonus and epilepsy, Gaucher’s disease must be considered among the lipidoses which cause this disorder. Parental consanguinity, Ashkenazi Jewish origins, and splenomegaly will suggest the diagnosis and an elevated serum acid phosphatase and Gaucher cells in the sternal bone marrow are virtually diagnostic. The demonstration of beta-glucosidase deficiency in fibroblasts is confirmatory.

I am grateful to Dr William Goody for permission to report this case and to Dr A. M. Halliday for his interest and advice. He also measured the cerebral evoked responses and supplied Fig. I. Dr Patricia Norman supplied Fig. 2. Dr B. D. Lake kindly performed the histochemical examination of the bone marrow and Dr A. D. Patrick performed the enzyme assays. The help of Dr Joseph M. Foley is also acknowledged.

REFERENCES


Progressive myoclonic epilepsy due to Gaucher's disease in an adult.

J O King

*J Neurol Neurosurg Psychiatry* 1975 38: 849-854
doi: 10.1136/jnnp.38.9.849

Updated information and services can be found at:
http://jnnp.bmj.com/content/38/9/849

**These include:**

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/