Cerebellar cortical degeneration with ovarian carcinoma

M. M. STEVEN*
M.B., Ch.B., M.R.C.P.

I. R. MACKAY*
M.D., F.R.C.P., F.R.A.C.P., F.R.C.P.A.

P. R. CARNEGIE†
B.Sc., Ph.D.

P. S. BHATHAL‡
M.B. B.S., Ph.D., F.R.C.P.A.

R. McD. ANDERSON‡
M.B. B.S., F.R.C.P.A., M.R.C.Path.

*The *Clinical Research Unit of The Royal Melbourne Hospital, and The Walter and Eliza Hall Institute of Medical Research, †The School of Agriculture, La Trobe University, and The ‡Department of Anatomical Pathology of The Royal Melbourne Hospital, Victoria, Australia*

Summary

A case is described of progressive cerebellar degeneration in association with ovarian carcinoma, with nearly 4 years elapsing between the onset of neurological illness and the discovery of the carcinoma. Neither treatment with prednisolone nor surgical removal of the tumour effected any improvement. CAT scanning late in the illness showed marked cerebellar atrophy. Histology at post-mortem showed complete loss of cerebellar Purkinje cells. The cerebrospinal fluid gave weak binding to multiple neural components in a solid-phase radio-immunoassay.

Introduction

A number of syndromes associated with cancer but not due to metastatic tumour deposits, the paraneoplastic syndromes, have been described (Brain and Norris, 1964; Joynt, 1974). In some instances, the ectopic production of hormones and hormone-like substances has been shown to be responsible but, in others, no cause was found. Neurological lesions are particularly common (Brain and Norris, 1964; Joynt, 1974; Croft, 1977; Brain and Henson, 1958; Vick, Schulman and Dau, 1969; Brain and Wilkinson, 1965; Croft and Wilkinson, 1965; Henson, 1970), and various clinical syndromes have been described. Peripheral neuropathy accompanying bronchial carcinoma is the most frequently recognized neurological lesion but subacute cerebellar degeneration which may accompany a variety of tumours is also well recognized, and a combination of central and peripheral lesions may be seen. The present authors describe pathological findings and results of

immunoassays on cerebrospinal fluid (CSF) in a woman presenting with clinical features of cerebellar and basal ganglia degeneration and later discovered to have ovarian cancer.

Case study

Clinical details

In May 1976, a 56-year-old woman presented with weakness of the legs and unsteadiness which had progressed over 21 months until she was confined to a wheelchair. The illness had commenced with back pain radiating to the right leg with associated numbness of the lateral border of the right foot. Initial improvement after corticosteroid therapy was not maintained, and left-sided calf pain, unsteadiness of gait and diplopia developed. In 1976, general examination was normal, and neurological examination showed tremor of the left hand, mild peripheral neuropathy and a right third-nerve palsy. Investigations including an X-ray of the skull, electroencephalogram and radioisotopic brain scan gave normal findings, but the CSF showed a lymphocytosis ($17/\text{mm}^3$) and an elevated protein concentration (0.53 g/l). A glucose tolerance test showed a diabetic curve and treatment by diet and sulphonylurea drugs was instituted. The diplopia resolved but the ataxia progressed and a posterior fossa tumour, possibly metastatic, was considered. Investigations of the gastrointestinal and urinary tracts for carcinoma were negative and the neurological symptoms were treated with physiotherapy and a trial of dexamethasone, but without benefit.

By January 1977, disability due to ataxia had progressed. Accordingly a CAT scan, pneumoencephalogram, analysis of CSF and a screen for

possible toxic chemicals were carried out, but the findings were again negative. A further CAT scan after 3 months showed prominent cisterns around the brain stem and enlargement of the fourth ventricle.

In November 1977, she was admitted to The Royal Melbourne Hospital, Victoria, Australia, complaining of dysphagia, weakness of the legs and unsteadiness. A symptomatic enquiry revealed the presence of minor post-menopausal bleeding. Diabetes was controlled by diet alone. Neurological examination showed a pill-rolling tremor and increased muscle tone with cog-wheel rigidity of the limbs indicative of disease of the basal ganglia, in addition to signs of gross cerebellar ataxia but general examination including a pelvic examination was negative. The only positive laboratory tests were a moderately elevated concentration of serum alkaline phosphatase (120 i.u./l, upper normal limit 90 i.u.) and an elevated level of immunoglobulin G in the CSF (0.06 g/l, upper normal limit 0.03 g/l). Cell-mediated immunity was depressed as judged by relative anergy on delayed hypersensitivity to skin tests to ubiquitous antigens (one positive response out of 4). A trial of L-dopa, instituted because of Parkinsonism, was not beneficial.

In May 1978, she was re-admitted with abdominal pain and vomiting, suggestive of intestinal obstruction. At laparotomy a left ovarian mass invading the sigmoid colon was resected and a colostomy formed. Histological examination showed a poorly differentiated papillary adenocarcinoma of the ovary and metastatic deposits were present on the peritoneum. Postoperatively chlorambucil was given. A proposed elective closure of the colostomy 3 months later was abandoned because of numerous omental metastases.

In November 1978, neurological disabilities attributable to disease of the extra-pyramidal system and cerebellum persisted, despite removal of the tumour, and at this time a CAT scan showed cerebellar atrophy (Fig. 1). Further courses of chlorambucil were given and 6 months after the first operation, the colostomy was closed at which time no peritoneal and omental deposits were evident. However, deterioration continued and death occurred 7 months after removal of the tumour and 52 months after the onset of neurological symptoms.

Post-mortem

There were widespread metastases from a papillary cystadenocarcinoma of the ovary, left hydronephrosis, multiple small infarcts of the lower lobe of the right lung and cerebellar cortical atrophy.

The brain weighed 1130 g. There was minimal atheroma of the arteries at the base of the brain.

FIG. 1. Computerized tomographic (CAT) scanning X-ray of brain showing marked atrophy of the cerebellum.

Serial coronal sections through the cerebral hemispheres, midbrain and brain-stem showed no abnormality and in particular no tumour deposits were found. The cerebellum showed mild generalized atrophy and severe atrophy of the uvula and nodules of the vermis and of the right cerebellar tonsil (Fig. 2). Histology of the cerebellar cortex showed diffuse and total loss of Purkinje cells with an associated gliosis (Fig. 3). Sections of the vermis, the uvula and nodule showed severe atrophy of the folia, the remnants of which exhibited thinning of the molecular layer and moderate loss of internal granular cells. In sections of the right cerebellar hemisphere the folia of the tonsil could not be identified, but the dentate nucleus was normal. The internal granular layer showed acute lysis presumed to be a terminal event accompanying diabetic acidosis. There was severe loss of neurones in both inferior olives associated with gliosis. The putamen, globus pallidus, thalamus and substantia nigra were normal.

Immunological studies in CSF

The CSF was tested by a solid-phase radioimmunoassay in Microtitre plates for reactivity against the following neural derivatives: human myelin basic protein (H-MBP), bovine central myelin, sonicated cells of the C6 rat glial cell line, and sonicated neonatal mouse cerebellar cells (SMCC), as described in Fig. 4. The procedure in principle is that described by Marvier, Jansen and Andriole (1979) and, as applied to neural antigens, by Linthicum *et al.* (1981). When the results are

expressed as picograms of protein A bound/25 μ l of CSF, a net binding of 0, 8.9, 10.1 and 10.0 was detected against bovine myelin, human myelin basic protein, SMCC and C6 cells respectively.

FIG. 2. The cerebellum is cut in the mid-sagittal plane through the vermis with the right cerebellar hemisphere orientated normally. The left cerebellar hemisphere is inverted. There is severe atrophy of the nodule and uvula of the vermis and generalized atrophy of the folia. The right tonsil (T) is shrunken and collapsed.

Figure 4 shows binding with one of the antigen preparations, SMCC. Whilst the magnitude of binding was very considerably less than with serum of rabbits immunized with the antigens used, the value for antibody to SMCC was higher than that found in CSF from 20 other patients with various neurological diseases, as reported elsewhere (Linthicum *et al.*, 1981).

FIG. 3. The cerebellar cortex shows complete loss of Purkinje cells associated with mild gliosis. (HE, $\times 150$).

Discussion

Neurological and neuromuscular disorders, as paraneoplastic syndromes of cancer, and unrelated to the presence of metastases, have been recognized for many years. Different patterns of neurological involvement have been distinguished (Brain and Norris, 1964; Joynt, 1974; Croft, 1977), but there is considerable overlap (Brain and Henson, 1958). Peripheral neuropathies and myopathy are recognized more frequently than CNS manifestations, and cerebellar degeneration is the most frequent central disturbance (Joynt, 1974; Vick *et al.*, 1969). This is most often associated with tumours of the lung and ovary (Brain and Wilkinson, 1965; Croft and Wilkinson, 1965), and it has been estimated

that some 50% of all patients with acquired progressive cerebellar disease have cancer (Henson, 1970).

FIG. 4. Solid-phase microtitre plate radio-immunoassay of cerebrospinal fluid (CSF), showing reactivity with sonicated neonatal mouse cerebellar cells (SMCC) as assessed by binding of ^{125}I -protein A (counts/min/well). ●—●, CSF of patient on plates coated with SMCC; ○—○, CSF of patient on an antigen-free plate representing 'background' reactivity; □—□, CSF of patient with prostate carcinoma on plates coated with SMCC. Cells were prepared by trypsinization (0.25% trypsin, 1 hr, 37°) followed by treatment with DNAase I and sonication. Microtitre wells were each coated with the equivalent of 2×10^5 cells in 100 μl of borate-buffered saline (BBS) for 4 hr. The wells were then washed with water and 200 μl of 1% bovine serum albumin (BSA) was added to saturate any non-specific binding sites on the plastic. To 100 μl of diluent (1% BSA, 0.05% Tween 20 in BBS) 25 μl of CSF was added for the 1/5 dilution, and the wells were kept for 6 hr at room temperature and washed; 1 ng of ^{125}I -protein A (30 000 counts/min) in 100 μl of diluent was added to the wells which were held overnight before washing and counting. The background binding of CSF to antigen-free wells was higher than that usually observed.

Combined cerebellar ataxia and extra-pyramidal disease, observed clinically in the present case, can be regarded as a rare association (Smith, Gonda and Malamud, 1958), and particularly so in association with neoplasia. In one detailed case study (Smith, Gonda and Malamud, 1958) including post-mortem on a male aged 63 years, severe degeneration and cell loss from the cerebellum and its centrifugal connections together with demyelination, cell loss and gliosis of the corpus Luysi and globus pallidus in the extra-pyramidal system were found; there was no family history of cerebellar ataxia nor was tumour apparent at post-mortem. Another case is cited (Brain and Wilkinson, 1965) of a male

patient, aged 40 years, with cerebellar dysfunction, parkinsonian facies and tremor associated with bronchial carcinoma; death occurred after 14 months and the neuropathological findings included the typical loss of Purkinje cells with astrocytosis of the cerebellar cortex and demyelination and perivascular lacunae affecting the globus pallidus. A further case, a male aged 45 years, developed parkinsonian facies, tremor and other neurological features 11 years after the onset of lymphoma; death occurred after 2 months, and demyelination and microglial proliferation involving the basal ganglia, and demyelination with loss of Purkinje cells and astrocytosis of the cerebellum were found (Woodhouse *et al.*, 1967). In the present case, despite the clinical features of extrapyramidal disease, the basal ganglia were histologically normal.

In the present case, the clinical features of cerebellar ataxia and Parkinsonism preceded the discovery of ovarian cancer by nearly 4 years. It is recognized that non-metastatic neurological complications may occur after or before the diagnosis of cancer (Brain and Wilkinson, 1965), but in the latter case the neurological symptoms rarely precede the cancer by more than 3 years. Although cerebellar degeneration revealed by CAT scanning is not diagnostically specific (Baker and Houser, 1976), when it occurs in the absence of conditions such as alcoholism, vascular disease or the familial ataxias, a search for visceral cancer should be undertaken. Whilst the course of central nervous disorders associated with carcinomas does not seem to be affected by removal of the tumour, one instance of remission after pneumonectomy for bronchogenic cancer is reported (Paone and Jeyasingham, 1980).

The aetiology of the paraneoplastic neurological syndromes remains unknown, but several mechanisms, not mutually exclusive, have been suggested (Joynt, 1974; Henson, 1970). The present author examined the concept that an autoimmune response could be involved on the basis that antigens of the tumour could be cross-reactive with antigens of brain cells. The older immunological literature contains references to cross-reactivity between components of brain, other tissues, and corpus luteum, testicle and kidney (Wilkinson, 1964; Wilkinson and Zeromski, 1965) and, in the mid sixties, complement-fixing autoantibodies to brain tissue in serum and CSF were observed in patients with paraneoplastic neurological diseases (Wilkinson, 1964). These autoantibodies were present only in patients with sensory carcinomatous neuropathy (Wilkinson and Zeromski, 1965), and further studies suggested reactivity with a neuronal antigen which was organ-specific but not species-specific, and was probably a protein present in the

microsome-rich fraction of brain homogenates (Zeromski and Wilkinson, 1966). Moreover, experimental studies (Coates and Carnegie, 1975; Flavell *et al.*, 1979) in guinea-pigs have shown that injection of acid extracts of cancer tissue may induce cell-mediated immune responses to basic protein of myelin, demonstrable by *in vitro* assays and cutaneous reactivity.

The radio-immunoassay studies on CSF in the present case, albeit positive, were not definitive. Firstly, there was a high non-specific background binding to the microtitre wells which is a particular problem with human as opposed to animal sera in this type of radio-immunoassay, and in this study could be related to the high protein content of the CSF. Secondly, the binding was very much weaker than that observed with sera of rabbits immunized with neural preparations (Linthicum *et al.*, 1981). Thirdly, the reactivity of the CSF was wide and not specific for cerebellar cells, and equivalent to that observed in various types of degenerative neurological disease (Linthicum *et al.*, 1981). Thus, in conclusion, the radio-immunoassay studies in this case of paraneoplastic cerebellar disease give evidence for an autoimmune response to neural antigens; whether this was causal rather than consequential to neural damage cannot be stated from the present findings.

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