Case Reports

Cerebral and Cerebellar Gliomas in a Case of von Recklinghausen's Disease with Adrenal Phaeochromocytomas

R. O. Barnard, M.B., and Edward R. Lang, M.D.*

The simultaneous occurrence of gliomas in the cerebellum and cerebrum of the same individual is rare. Of the possible mechanisms responsible, that of multiple primary tumours arising independently has always failed to gain much support. Russell and Rubinstein pointed out that this concept would be more acceptable if it were possible to demonstrate multifocal benign cerebral astrocytomias, but to their knowledge this had never been established; in the majority of cases reported the tumours were of so malignant a nature that the deposits could well be metastatic.

In the case we describe a diffuse astrocytic glioma of the cerebrum and mesencephalon was accompanied by nodules of glial tumour in each of the cerebellar hemispheres in a patient with cutaneous von Recklinghausen's disease and bilateral phaeochromic tumours of the adrenal medulla.

Case Report

50794, D.C., a 58-year-old white female, was referred for neurosurgical opinion to Mr. Valentine Logue at the Maida Vale Hospital for Nervous Diseases on May 3, 1962, from the Amersham General Hospital, where she had been admitted for the investigation of headaches, progressive dementia, and unsteadiness of gait which she had suffered for some 6 months. Lumbar puncture had yielded normal cerebrospinal fluid. On arrival at Maida Vale Hospital she volunteered no complaints but admitted on direct questioning to using words incorrectly, occasionally inventing neologisms, and impairment of memory for recent events. No family history of disease of the nervous system or skin could be obtained, but it was noted that one of her three children bore nodules on the skin of his face.

Examination. The patient was fully conscious and reasonably co-operative, but her intellectual impairment was such that only a very simple conversation was possible. She was disoriented in time and place and while there was some degree of expressive dysphasia, she could use her pen correctly (she was right-handed) and read letters and numerals.

The fundi were normal; there was bilateral ptosis and the pupils were dilated—the left larger than the right. Reaction to light was normal. There was marked impairment of voluntary gaze in all directions. There was no true nystagmus. The jaw jerk was exaggerated. A right-sided grasp reflex was present and a tetraparesis with spasticity more marked on the right and weakness more marked on the left side; the right plantar reflex was extensor, the left equivocal. Sensation to painful stimuli and sense of vibration were unimpaired, but other modalities could not be tested. Gait could not be examined. The heart, lungs and abdomen were normal. Blood pressure was 150/90. There were multiple cafe au lait spots and pedunculated nodules in the skin of limbs and trunk. A clinical diagnosis of midline glioma and von Recklinghausen's disease was made.

Investigations. Haemoglobin was 12.3 gm. per cent (84 per cent). Count of white blood cells was 12,100 per c. mm. (differential: neutrophils 84 per cent, eosinophils 1 per cent, lymphocytes 12 per cent, monocytes 2.5 per cent, basophils 0.5 per cent) and a sedimentation rate of 5 mm. per hour (Westergren). Wassermann reaction was negative. Electroencephalography showed an abnormal record reported as "suspicious of an anteriorly placed midline lesion" (Dr. M. Painter). Roentgenograms of chest and skull were normal. Bilateral carotid angiography (May 8, 1962) suggested considerable ventricular dilatation. Ventriculography (May 9) confirmed the hydrocephalus and showed narrowing of the back of the 3rd ventricle from side to side. Air would not pass through the aqueduct. Myodil ventriculography showed that the aqueduct was narrow and irregular. The report (Dr. G. H. du Boulay) concluded that the appearance of the aqueduct could be explained only on the basis of an infiltrating brain-stem lesion or congenital narrowing, and the narrow back of the 3rd ventricle would be consistent with an infiltrating lesion. Protein in the ventricular fluid was less than 10 mg. per cent.

Course. During the week following admission the patient's condition deteriorated. On May 9 Mr. Logue considered that the radiographic findings were most probably caused by a brain-stem glioma but a midline meningioma of the clivus or bilateral acoustic neurofibromas were possibilities that had to be excluded. However, the latter was an unlikely diagnosis in view of the normal amount of protein in the cerebrospinal fluid and the absence of symptoms of the 8th nerve.

Operation. It was decided as a last resort to explore the lesion and, if inoperable, ventricular drainage of the hydrocephalus would be instituted. The same afternoon exploration was made through a posterior temporoparietal flap. The temporal lobe was elevated, the tentorium was incised and no lesion of the cranial nerves or clivus was found. The pons appeared swollen. It was felt that no surgically treatable lesion was present and closure was made. The ventricles were drained.

The patient expired on the night of the operation.

 Necropsy was performed within 24 hours of death. The external appearances were typical of von Recklinghausen's disease with many cafe au lait spots (largest 7
mm. in diameter) and approximately 50 soft pedunculated tumours of the skin (largest 3 cm. in diameter); the majority of these lesions were on the front of the chest and abdomen. No relevant changes were found in any of the viscera except the adrenal glands. These were enlarged (right weighed 75 gm. and left 25 gm.) by the presence of tumours of similar appearance (Fig. 1). In each of the glands the adrenal cortex and medulla were normal up to the point at which the cortex was stretched over the tumour, forming most of the intact capsule investing the growth. The cut surface of each tumour was terra-cotta brown streaked with dark areas of haemorrhage (the right was 5 cm. in diameter, the left 3 cm.). When placed in 10 per cent formalin, the brown colour of the tumour diffused at once into the fixative.

Both hemispheres of the brain (total weight 1425 gm.) were swollen and there was a moderate degree of herniation of the cerebellar tonsils; the uncus was grooved on both sides. No tumours were present on nerve roots. On the under surface of the left cerebellar hemisphere there was a hard, very pale grey nodule 7 mm. across, whose centre was 10 mm. lateral to the midline. On the under surface of the right cerebellar hemisphere there was a similar nodule 5 mm. across, 20 mm. from the midline. The spinal cord and nerve roots were examined and removed via the anterior approach; no abnormality was seen. After fixation in formalin the brain was sliced in the coronal plane; in the anterior slices there was oedema of both hemispheres, but more in the left than in the right and the septum pellucidum was shifted across the midline towards the right side. There was diffuse, pale grey, glial hypertrophy or tumour involving the thalamus on both sides, which extended to the subthalamic nuclei (Fig. 2). The head of the right caudate nucleus was replaced by a gelatinous glial mass about 8 mm. in diameter. The exact confines of the process could not be determined. The mid-brain was swollen from infiltration by pale grey firm tissue that was especially obvious around the narrow aqueduct; this did not appear to extend below the level of the mid-pons.

**Histology.** Microscopical preparations of several levels of spinal cord, nerve roots, posterior root ganglia and various viscera show no relevant changes. The tumours of the skin are typical neurofibromas with elongated cells containing slender nuclei distributed through a faintly collagenous matrix. The adrenal tumours are composed of solid cords of large polygonal cells, often with a bulky cytoplasm filled with granules staining brown in haematoxylin and eosin preparations after formalin-chromate fixation and blue by Gomori's method. Fine strands of connective tissue separate groups of neoplastic cells. A few multinucleated giant cells are present but cells in mitosis are very rare. The tumours show all the characteristics of phaeochromocytomas and no features that suggest malignancy.

The cerebral tumour is a diffuse astrocytic glioma (Fig. 3). The neoplastic cells have small oval or rounded vesicular nuclei and, for the most part, the body of the cell is indistinguishable. A few cells, however, are typical "gemistocytes" and rarely are there multinucleated cells. Some fine short glial fibres accompany the neoplastic cells, but the over-all picture is of paucity of glial

---

**Fig. 1.** Phaeochromocytoma of the right adrenal gland.

**Fig. 2.** Coronal section of cerebrum showing diffuse enlargement of both thalami by a glial tumour. The head of the right caudate nucleus is replaced by a glistening nodule.
fibres. With Mallory's phosphotungstic acid haematoxylin the mass of the tumour stains dull pink, intersected with a little dark blue streaking. Mitotic figures are not seen and there are no areas of haemorrhage or necrosis. In the most cellular parts of the tumour there is proliferation of capillary blood vessels but there are none of the groups of thick-walled vessels that are seen in malignant gliomas. The pre-existing structures of nervous tissue are widely infiltrated but not destroyed; often the astrocytic cells are grouped around pre-existing nerve cells. In some areas Rosenthal fibres are seen, but there is no calcification. There is a tendency for the cells to be arranged in interlacing bundles, forming a pattern resembling a "Schwannoma." This proliferation occupies much of the thalamus on both sides, where it reaches its maximum intensity, and infiltrates the subthalamic nuclei, substantia nigra and red nuclei. It is limited laterally and superiorly by the internal capsule on whose medial aspect slight proliferation of astrocytes of the tumour is present (Fig. 4). In celloidin-embedded sections of the hemispheres the corpus callosum, centrum semiovale, and cortex from the hippocampal, parietal and occipital regions appear tumour-free. The head of the right caudate nucleus is largely replaced by

Fig. 3. Thalamic tumour, showing cells with astrocytic nuclei and short glial processes. Phosphotungstic acid haematoxylin, × 600.

Fig. 4. Edge of thalamic tumour, above and to the right, reaching medial aspect of internal capsule (on the left). Haematoxylin and eosin, × 160.
tumour (Fig. 2). In several areas the growth has breached the ependymal lining of the 3rd or the lateral ventricle with the formation of tiny projecting glial nodules. Beside the margin of the 3rd ventricle there is diffuse infiltration of the pre-optic nuclei. Where the glioma gains the meningeal surface it forms a focus of fibrillary thickening, but there is no extensive spread in the meninges.

The mid-brain at the level of the decussation of brachium conjunctivum is diffusely swollen and the aqueduct is narrow, distorted and shifted towards the right. Throughout the section at this level there is infiltration by proliferating glial cells; only a portion of the left cerebral peduncle is spared. The tumour is most dense around the aqueduct and here glial fibres are abundant. Where it reaches the meningeal surface it forms a dense glial network over the dorsum of the mesencephalon. At the rostral end of the pons the roof of the aqueduct is deformed by a rounded nodule of glial tumour compressing the ependymal lining and tending to bulge into the cavity (Fig. 5). Laterally this extends into the brachium conjunctivum; the medial longitudinal bundle and pontine fibres are spared. The appearance of the tumour is similar to that in the thalamus: the nuclei are mainly small oval and vesicular, and glial fibres vary in amount. Where the cells are clustered around the numerous small blood vessels there is more variation in their shape and size; the greatest degree of anaplasia is seen in the meningeal coating. No areas are found, however, that could be interpreted as glioblastoma. The tumour does not extend into the mid-pons or medulla.

The cerebellar nodules are astrocytic gliomas (Fig. 6). There is diffuse growth in the white matter which becomes more obviously pilocytic as it spreads through the granular and molecular layers. Cells arranged in parallel form bundles of fibres streaming vertically through the molecular layer onto the pial surface where there is dense, localised infiltration (Fig. 7). In these areas the nuclei of the Bergmann astrocytes in the Purkinje cell layer are abnormally large and numerous; the fibrillary cells forming the tumour extending into the leptomeninges appear to be derived from them. There is some new formation of collagenous fibres in the infiltrated leptomeninges. Astrocytic gliosis in the molecular layer and white matter is diffuse and extends beyond the area involved in the meningeal spread, which is well localised. The appearances are those of benign tumour arising from pre-existing glial cells and do not suggest spread from elsewhere. Indeed, these glial proliferations could be interpreted as developmental errors (hamartomas) on the borderlines of dysplasia and neoplasia but, although they are at present small, their diffuse character and infiltrative ability point to a truly neoplastic potential.

**Discussion**

The association of phaeochromc tumours of the adrenal glands with neurofibromatosis is well-recognised. Rosenthal and Willis discussed early reports and added 1 case of bilateral tumours. Since then several case reports have appeared and the subject has been reviewed by Glushien et al. These authors estimated an incidence of 10 per cent of phaeochromocytomas being complicated by neurofibromatosis, but this figure has been criticised as too low. On the other hand, in only 1 of the 228 patients with neurofibromatosis studied by Crowe et al. was a phaeochromc tumour found post mortem.

Since 1910, when Verocay reported a case in which meningiomas and neurinomas co-existed with frontal and brain-stem gliomas, several authors have described neuro-ectodermal tumours in patients with neurofibromatosis. These have been collected and classified by David et al. who added several reports of their own cases, including examples of astrocytic tumours of cerebrum and cerebellum.
In the case we have recorded, the cerebral and mesencephalic lesions resemble those described by Nevin in his papers on gliomatosis cerebri and thalamic hypertrophy. In the first of these papers, Case 2 showed the cutaneous pigmentation of von Recklinghausen's disease, and Case 1 of the second paper, a girl aged 7, was born with café au lait spots. Russell and Rubinstein approximated Nevin's "gliomatosis cerebri" with "diffuse cerebral astrocytoma" and they considered that the diffuseness of the process supports Scherer's contention that neoplasia has arisen over a wide field.

The cerebellar lesions closely resemble the diffuse astrocytoma that is illustrated by Russell and Rubinstein on page 118; in this tumour the white matter was infiltrated by stellate astrocytes which became of piloid form close to the pia and leashes of these cells extended as bridges to the infiltrated leptomeninges. It was commented that the appearances suggested a "field origin" of the tumour. Similar lesions were described by de Ajuriaguerra et al. as "meningo-cerebellar gliosis"; there was overgrowth of cerebellar astrocytes spreading to the infiltrated meninges by bridges and the proliferation was of all degrees of intensity up to that of a glioma. Cutaneous neurofibromatosis was present in these cases; the authors concluded the condition was a form of dysplasia.

Solitaire described a case of cerebral and cerebellar astrocytomomas occurring in the same individual and has re-assessed previous case reports. He found that this combination was very uncommon.

Recently, Batzdorf and Malamud have examined the problem of multiple gliomas and out of 209 specimens found 5 multiple tumours: these were glioblastoma multiforme. They discussed various hypotheses, particularly the Cohnheim theory of rests of primitive cells and the two-fold process suggested by Willis that in the first stage of neoplastic transformation a wide field becomes susceptible and in the second stage proliferation occurs which may be at several sites. In our case, this is the most acceptable explanation.

Summary

A patient is described with von Recklinghausen's neurofibromatosis, phaeochromic tumours of both adrenal glands, and diffuse astrocytic tumours of cerebrum and cerebellum.

It is considered that this uncommon combination suggests that neoplasia can operate over a wide field with the production of multiple independent primary tumours derived from neuroectoderm.

We wish to thank Mr. Valentine Logue for his encouragement and help in placing his notes at our disposal, Dr. W. H. McMenemey (Maida Vale) and Dr. Paul C. Bucy (Chicago) for criticism and advice. We are indebted to Mr. Gordon Cox together with others of the technical staff of the Maida Vale Hospital laboratory for the photographs and histological preparations.

References

2. Batzdorf, U., and Malamud, N. The problem of
Multiple Tumors in Same Individual


