BRAIN STEM GLIOMAS CAUSING HYDROCEPHALUS IN TWINS
WITH VON RECKLINGHAUSEN'S DISEASE*

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In the plethora of medical literature on von Recklinghausen's multiple neurofibromatosis, there are no necropsy records of affected uniovular twins. With a report of such cases, it will be shown that the location and nature of brain tumors in this syndrome rather than being a random development may be specifically determined in the earliest stages of fetal differentiation. In this study the published cases of twins with neurofibromatosis will be summarized and the clinical reports and necropsy findings presented of monozygous brothers with this disease who were followed from birth to death in the University of Oregon Medical School Hospitals and Clinics.

Nine clinical reports of twins with neurofibromatosis have been published. In 1926, Siemens stated that the condition had never been reported in twins and theorized about the genetic data obtainable from such cases (1). Blotevogel (2), in a discussion of neurofibromatosis as a dominantly transmitted trait mentioned in passing such affected twins, but gave no data on either. Curtius (3), parenthetically told of observing a pair of twins with this condition. In 1936 Leers (4) reported 60 year old twin sisters with the classic form of neurofibromatosis. They had no family history of the disease, were not proven to be uniovular and neither was necropsied. A clinical report by Grohman of 28 year old affected identical twins was unobtainable. Geyer and Pedersen (5), however, in summarizing Grohman's cases mentioned no histologic or autopsy data. Davis (6), wrote of a non-identical twin with a family history of neurofibromatosis. This 4 year old girl had an optic nerve tumor and café au lait spots, but her twin brother had no signs of the disease. The same year Loftis (7) wrote of observing 42 year old sisters with a family history of von Recklinghausen's disease who appeared to be identical twins and who each had a single café au lait spot with multiple cutaneous tumors. One had loss of bilateral hearing, but no further investigation was reported. Dresner and Montgomery (8), in 1949, related the clinical findings of 13 year old twin girls with the syndrome and bilateral optic nerve atrophy who had a family history of the disease. Gliomas of the second cranial nerves of both were suspected but not proven. Pollet and Pollet (9), reported twin sisters examined at the ages of 20 and 30 years, both of whom apparently had thromboses of their left ophthalmic veins. One sister had the abortive form of neurofibromatosis, but no data on family history, uniovularity or of other detailed examinations were given. The latest report is by Troch (10) who, in 1953, wrote of 18 year old, presumptively identical, twin girls with a maternal history of cutaneous tumors. He observed café au lait spots in each but no neurofibromata. One sister had epilepsy progressing from a petit mal type to

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typical grand mal convulsions. Cardiazol stimulation provoked a generalized convulsion in her twin.

Although none of these twins had histologically verified brain tumors, there are reports of these tumors in twins without neurofibromatosis. Some of these identical pairs without von Recklinghausen's disease have been concordant and have had similar brain tumors, but other twins have been discordant for the condition (11).

REPORT OF CASES

Family History (fig. 1): The twins' paternal grandmother had café au lait spots, but no other evidence of the syndrome at death. Her eldest son by her first husband had hearing difficulty at the age of 13 years from an undetermined cause and became almost totally deaf. The other son had bilateral retinal detachment with no clinical indication of optic nerve gliomas. He and his children denied overt stigmata of neurofibromatosis, but one of his 6 grandchildren has café au lait spots.

Two girls and the youngest boy from the grandmother's second marriage denied any signs of the syndrome in themselves or their children. The twins' father and older brother had café au lait spots. At the age of 14 years this brother had a brain stem astrocytoma removed, and 7 years later was in excellent health.

Birth: The boys were delivered without trauma after an uneventful full-term gestation and weighed 6 pounds, 7 ounces, and 6 pounds, 2 ounces at birth. The birth report stated they had a single placenta and a single amnion. No microscopic examination was made of the fetal membranes. The twins had identical hair and eye coloring and facial characteristics, and prior to an endocrine upset in one, conformed in body structure. Both were of blood group A and were Rh Positive. By these accepted criteria of uniovularity (12), they were monozygous twins. They were concordant with respect to von Recklinghausen's disease and brain

Fig. 1. Diagram illustrating the occurrence of neurofibromatosis in the descendants of the twins' paternal grandmother.
stem gliomas, but apparently discordant as to optic nerve gliomas at death. Each was breast fed and gained weight rapidly and developed normally for the first 4 years. Both had numerous café au lait spots on their trunk and thighs.

Case One: When twin number one was 4 years old, he began to grow far more rapidly than his brother. His genitalia began to mature so that when he was first admitted to this hospital at the age of 7 years for pneumonia he had a pubertal sexual development. He then weighed 57 pounds, while his twin weighed 60 (fig. 2). He rarely had headaches, and there was no history of convulsions. The blood pressure ranged from 140 to 170 mm of mercury systolic and 98 to 120 mm of mercury diastolic in both arms and was 210/124 and 180/120 in his legs. The fundal vessels had a glistening silver sheen, and there was no papilledema or hemorrhage. All of the cranial nerves were intact. The tendon reflexes were uniformly hyperactive with bilateral sustained ankle clonus. The patient had poor coordination, a bilateral intention tremor and his general intellectual level was recorded as "low".

Examination: Repeated blood and urine examinations were within normal limits. Cerebrospinal fluid pressure was normal. Electrocardiograms were normal. Assays placed his gonadotropins and estrogens at a 3 to 5 year post-pubertal level. Roentgenograms showed a bone development of a 9 year old male. An electroencephalogram was read as normal and pneumoencephalogram demonstrated no ventricular enlargement. On skull roentgenograms, the sella turcica was of normal size, shape and density. There were no intra cranial calcifications or abnormalities in the cranial bones.

Each adrenal gland was biopsied and was considered to be normal. The child's hypertension and macrogenitosomia were then diagnosed as secondary to a tumor of the pineal or of the floor of the third ventricle, but surgical exploration was not advised.

Course: Seven years later at the age of 14 years when the patient entered this hospital for intermittent left flank pain and hematuria, he also complained of progressively more severe and frequent headaches, and was extremely nervous and irritable. He had become "pale, tired and weak" during the previous 2 months, and despite a good appetite, had lost 20 pounds during the past year.

The blood pressure was now 232 mm of mercury, systolic and 125 mm of mercury, diastolic. His head was enlarged. There were fine tremors of the extremities and many café au lait spots, but no skin tumors. Long standing hypertensive retinopathy with bilateral exudates and hemorrhage associated with papilledema and retinal edema were present. Visual fields were normal. A loud, harsh systolic murmur was heard over the precordium. The genitalia were of adult type. Examination of the cranial nerves was reported as normal. The upper and lower extremities were hypertonic with rigidity increased on the left. There was weakness of all arm muscles with fine tremors of the fingers. There was a left extensor plantar response and a left-sided hyperesthesia with bilateral diadoskiinesis. A Romberg test was negative. The gait was mildly spastic; the patient walked unsteadily and deviated to the right.

A series of laboratory examinations showed no abnormality other than an anemia of 8.6 grams of hemoglobin per 100 ml. of blood, and 2.89 million red blood cells per cubic mm. of blood. The cerebrospinal fluid had 181 cells per cubic mm., most of which were lymphocytes. A twenty-four hour urine ketosteroid excretion was 18.2 mms. Two regiun tests were normal. Roentgenograms showed a calcific density associated in the left kidney. The skull was enlarged with exaggerated and prominent convolutional markings and separated lambdoid sutures. The dorsum sellae appeared intact. No evidence of abnormal calcification was seen within the skull. An electroencephalogram showed activity above the usual range. Electrocardiograms demonstrated left ventricular hypertrophy; at ventriculography 500 cc. of fluid was found in each lateral ventricle, and the fourth ventricle was completely blocked.

Nine days later the boy developed generalized left-sided clonus. At craniotomy a firm solid tumor pillar projected through the lateral right wall of the fourth ventricle and another smaller pillar bulged from the left side of the floor. These masses completely occluded the ventricle, but excision biopsies of each relieved the block. The boy's blood pressure gradually decreased and he died 38 hours after surgery.

Post Mortem Findings: The body was embalmed and then autopsied 41 hours after death.
Fig. 2. The twins at the age of 7 years. The first boy's microgenitosomia and the café au lait spots on each are evident.

The head was perceptibly enlarged and the genitalia were of adult size. There were numerous café au lait spots, but no tumors, on the back and abdomen. The heart weighed 320 grams and measured 14 cm. in transverse diameter. The left ventricular wall averaged 2.5 cm. in thickness. The coronary arteries were sclerotic. The adrenals together weighed 20 grams, but con-
tained no tumors. The left renal artery had a 1 cm. calcified aneurysm adjacent to the pelvis. Both testes were of adult size, and the prostate and seminal vesicles mature.

The calvarium was thinned to 3 mm. in some areas. Neither optic nerve was enlarged, the pituitary gland was grossly normal and all of the cranial nerves appeared tumor free. The spinal cord and filum terminale were normal. The brain was large, weighing 2050 grams and was firm. The cerebral sulci were narrow, and the gyri flattened. No tumor was evident externally in the brain stem. One cm. thick transverse sections of the brain revealed greatly dilated lateral ventricles with a thin cerebral cortex throughout. The third ventricle was distended, but its floor not protuberant. The hypothalamus was compressed but externally normal. The pineal was small, membranous and difficult to distinguish. There was post-surgical hemorrhagic destruction of the left medial portion of the brain stem adjacent to the blood filled fourth ventricle. The walls of the fourth ventricle and the adjacent cerebellum, which had been biopsied, were distorted and there could be no tumor delineated.

**Microscopic Examination:** There was an acute bronchitis and a patchy bronchopneumonia. The wall of the left ventricle of the heart contained many hypertrophied muscle fibers. The cortex of each adrenal was thickened, the medulla normal, and the intima of the pericardial vessels was hyperplastic. In each kidney there were arteriosclerotic and arteriolosclerotic vessels and a patchy glomerular fibrosis. Spermatoogenesis was present and the prostate had an active gland structure. The pituitary gland was normal. No section was taken of the pineal gland or of either optic nerve.

Twenty-one sections from representative areas of the brain showed several abnormal processes. Hyperplasia of the glial elements in the basal ganglia and subependymal areas was widespread and there was a diffuse gliomatosis of the cerebrum. Despite the hemorrhage and meningeal inflammation in the brain stem, several areas in the floor of the fourth ventricle clearly showed neoplasms. Sections of the spinal cord reflected only a mild postoperative cellular reaction in the meninges.

Only the surgical material had adequate tumor for study. These biopsy sections of the brain stem tumor, stained with hematoxylin and eosin, had good detail, but phosphotungstic acid hematoxylin and silver stains were unsatisfactory. The small sharply delineated neoplasm, a spongioblastoma, contained many clumped eosinophilic cells with a smudged irregular Hyaline appearance, intermingled in the normally staining astrocytes and oligodendroglia. These pleomorphic degenerated spongioblasts varied from small and oval to large and elongated ones, depending on the plane of section, but with hematoxylin and eosin stain all lacked distinct nuclear chromatin, cytoplasmic granules or evident cellular processes (fig. 3). Mitoses and giant cells were absent. Special stains of this formalin-fixed tissue stained these degenerated forms only faintly, nevertheless their precise resemblance to apparently identical cells throughout the other twin’s tumor was remarkable.

**Course:** At the age of 7 years, during his brother’s hospitalization, twin number two had a slightly enlarged skull on roentgenograms and a blood pressure of 150 mm. of mercury systolic over 100 mm. of mercury diastolic. At about the age of 16 years two years after his twin’s death he began to experience intermittent, progressively intense headaches. Four days before admission he developed a severe headache which became increasingly painful and was followed by vomiting. The day he entered this hospital he had generalized convulsions, was incontinent of urine, drowsy and difficult to arouse.

**Examination:** In the hospital he was extremely lethargic and responded only to painful stimuli. Blood pressure was 138 mm. of mercury systolic over 90 mm. of mercury diastolic. He was normally developed for his age of 15 years. His head was large and he had multiple café au lait spots, but no skin tumors. Retinal vessels were normal and optic disks well outlined. There was no disparity of the optic disks. His cranial nerves seemed intact. He responded to pain by withdrawing his extremities, and there was no increased resistance to passive stretching. Deep tendon reflexes were active in both arms, and equal and active in each leg with bilateral clonus. There was violent withdrawal to plantar stimulation.

Examinations of blood and urine were not significantly abnormal. The opening cerebrospinal fluid pressure was 260 mm. of water, and there were 5 cells per cubic mm. of fluid. Roentgenograms showed cranial enlargement and exaggerated convolutional markings with promi-
nent suture lines. The sella turcica was flattened and its anterio-posterior diameter was increased. The dorsum sella was small and no intracranial calcification was noted. An electroencephalogram displayed activity above and below the usual range of frequency.

For a few days the boy continued to be drowsy and lethargic, and had tonic convulsions. A craniotomy was performed and a firm tumor was found occluding the fourth ventricle. No biopsy was taken, but a shunt was placed to pass the obstruction. Postoperatively the patient's blood pressure gradually decreased and he died 29 hours after surgery.

Post Mortem Findings: The body was autopsied unembalmed four and one half hours after death. Enlargement of the head, surgical scars, numerous café au lait spots and adult genitalia were observed. There were no tumors in the skin, abdomen, or thorax. Each lung showed several discrete areas of aspirated blood. The heart weighed 350 grams and had an average left ventricular wall thickness of 1.8 cm. Both adrenal glands were small but normal. The stomach was dilated by more than a liter of blood from multiple mucosal ulcerations. There was bloody fecal material in the small intestine, but not in the colon. All other viscera were normal.

The calvarium had an average thickness of 8 mm. The pituitary gland appeared normal. The spinal cord and filum terminale were free of tumors. The brain was large, weighed 1820 grams, and was very firm. Each cerebral hemisphere had narrowed sulci and flattened gyri. There was a 1.2 cm. long and 1 cm. wide smooth ovoid enlargement of the right optic nerve but the left nerve was normal. On the ventral surface of the right side of the brain stem, surrounding cranial nerves IX, X, and XI, was a smooth glistening white mass extending to, but not invading, the cerebellum; 1 cm. transverse sections showed dilated lateral ventricles and a thin cerebral cortex.

The third ventricle was enlarged, its floor was protuberant and paper thin and the hypo-
thalamic area was somewhat compressed, but otherwise normal. The pineal body was small, firm and blunt. There was minimal hemorrhage into the fourth ventricle, but an elliptical discrete, white, firm mass had extended into the ventricle from the area of the fasiculofusiform longitudinalis dorsalis in the left side of its floor. Posteriorly, the tumor reached the nucleus gracilis at the base of the fourth ventricle and there, only partially filled the chamber. Near the rostral portion of the inferior olivary nucleus it widened to 6 mm and forced the nodule laterally to occlude the ventricle. Anteriorly, the growth again narrowed and could be seen only as far as the cerebellar aqueduct.

Microscopic Examination: Each lung had a patchy bronchopneumonia and areas of aspirated blood. The stomach mucosa was focally eroded and the other viscera were without significant change. Both lobes of the pituitary gland and pineal body were normal.

The brain was fixed in 10 per cent formalin for 6 weeks and the tissues embedded in paraffin and stained with hematoxylin and eosin, a Protargol modification of Bodian's Silver Stain and also a phosphotungstic acid hematoxylin stain. Representative sections from all parts of the brain had no generalized astrocytic proliferation. Severe foetal degeneration and neuronophagia were observed in the inferior olivary nucleus probably due to ischemia. Scattered glial nodules were present in the cerebellum. There was an intense acute inflammation in the leptomeninges of the spinal cord and brain stem.

A poorly demarcated small fusiform tumor originated in the left side of the floor of the fourth ventricle, invaded the ventricle, and extended upward eneurohoming as far as the choroid plexus. It spread laterally into the subarachnoid space as a thin tumor plate to form a mass around the cranial nerve roots, but did not invade these nerves. The histology of the tumor was similar at different levels and had a pattern throughout of a subependymal spongioblastoma, a diagnosis the Armed Forces Institute of Pathology confirmed after complete review of the autopsy (13). In the tumor, mixed with normally staining glial cells, there were clumps and elongated bands of irregular pale eosinophilic cells having an identical appearance to those in the other twin (fig. 3). In silver preparations these stained a light golden brown and often had distinct nuclei, granular cytoplasm and definite unipolar and bipolar processes (fig. 4). Their size and shape varied widely with their plane of section. The hyaline transformation of these multiform spongioblasts as studied in hematoxylin and eosin stained preparations corresponded well with "a typical sort of degeneration" in which "the entire cell body... is... transformed into homogeneous densely staining material" described by Bailey (14) in a series of 32 spongioblastomas. Other features of our tumors, such as linear bands of these cells and modularity of their hyaline material, are also described in this review. Four of Bailey's cases also had an associated von Recklinghausen's neurofibromatosis. This patient's neoplasm had less distinct boundaries than that of his twin brother, but like it, contained no evident mitoses or giant cells. This tumor also had a completely different pattern than the brain stem astrocytoma in the twin's older brother.

Two processes were evident in the optic nerve tumor; a neoplastic glial proliferation in the funiculi and an arachnoid thickening and glial invasion. Centrally, the neoplasm was less differentiated with obliteration of septa and an overgrowth of glial cells. These cells were principally astrocytes exhibiting loose elongated nuclei containing clustered chromatin, but no evident mitotic figures. Many small round dark oligodendroglia cells were also scattered throughout the funiculi. There was mild vacuolization of the ground substance, but fewer spaces were evident than in tumors of the same stage pictured in Davis' work (6). Clusters of oval cells and multinucleated forms were absent. Peripherally, the fibrous septi were distinct and the funiculi intact. Here, however, there was an evident condensation and thickening of the glial network in the periphery of the funiculi (fig. 5). Phosphotungstic acid hematoxylin stains demonstrated thick mats of dark blue glial fibers interspersed throughout the brick red fibrous tissue of the pia and arachnoid. The dura was not invaded. Sections through the chiasm exhibited no glial proliferation, and the left optic nerve was normal. Although the general pattern of this tumor corresponded to Davis' third stage (6), the central area had advanced glial proliferation and septal destruction.
Fig. 4. Tumor in fourth ventricle, twin §2. Scattered large spongioblasts with dark nuclei and granular cytoplasm. Bodian silver stain; × 560.

Fig. 5. Felt-like layer of glial fibers around the periphery of the funiculi and increased number of glial cells in the optic nerve glioma of twin §2. Bodian silver stain; × 175.
DISCUSSION

These cases present an unusual opportunity to study the development of brain tumors in neurofibromatosis. To emphasize their significance, the principal characteristics and etiologic theories of this syndrome will be reviewed and three unusual aspects of these cases discussed.

Von Recklinghausen’s neurofibromatosis is a dominantly transmitted hereditary condition in which tumors of neuro-ectodermal origin may occur in various tissues and organs. The tumors may produce secondary changes in other structures. The classic form of the disease is characterized by peripheral neurofibromata and café au lait spots; the abortive form by the spots and occasional central lesions. The incidence is given as one in 2500 to 3000 live births (15). The neurinomas may be pedunculated growths within the skin, subcutaneous tumors, or they may be intracranial or within a body cavity. Café au lait spots are caramel-colored macular patches of melanotic pigment, more prevalent in unexposed areas of the body. They may be evident in the newborn, but appear characteristically during the first decade. The abortive form of the disease may be diagnosed solely by the presence of 6 spots if each is 15 mm. across (15). Central nervous system lesions have been described in various parts of the brain and spinal cord. These may be diffuse or localized, and their complexity and variability are almost limitless.

Several investigators have postulated a basic metabolic defect underlying the varied manifestations of the syndrome. Penfield and Young (16), in 1930, stated that an irritating or stimulating influence is exerted on different tissues causing hyperplasia and occasional subsequent neoplasia. They suggested that a congenital defect may produce the irritation. In 1949, Lichtenstein (17) characterized the disease as one involving neuroglia, myelin, meninges, capsule cells and connective tissue of the cerebrospinal ganglia, supportive tissues of the nerves, and protective and supportive tissue of the epidermis. He believed these neuro-ectodermal derivatives underwent focal hyperplasia and neoplasia to produce the characteristic manifestations of the syndrome. A primary degeneration of the neural elements releasing stimulating biochemical products that cause proliferation of supportive structures such as neuroglia, meninges or endoneurium was postulated by Davis (18).

Pigmented cells might be added to these other neuro-ectodermal derivatives since their neural crest origin has been established in lower forms (19). If their proliferation to cause café au lait spots is similar to that of the other stimulated structures, however, more reports of malignant change would be expected (20).

Macrogenitosomia praecox is an unusual occurrence in von Recklinghausen’s disease, although it has been described with hydrocephalus by Piotti (21). The first case here fulfilled the classic criteria for pubertas praecox of central nervous system origin (22). This was confirmed at autopsy and the absence of a pinealoma, a third ventricular cyst or tumor and any pituitary abnormality was established. Despite the small size and membranous character of the pineal body, which some investigators thought to be a causative factor, others believed that it played no role in the patient’s early maturation (23). Several authors in ex-
tensive reviews of precocious puberty with hydrocephalus have postulated a
compression of the posterior hypothalamus or the caudal part of the dienecpha-
lon causing interference with mechanisms normally inhibiting the production of
gonadotropins (24). Our case would seem most clearly explained by this theory.

The relation between von Recklinghausen's syndrome and optic nerve gliomas
is an established one, first having been stressed by Davis (6). Marshall, in 1954,
reviewed and supplemented Davis' work emphasizing again that these tumors
are associated with the abortive form of neurofibromatosis which may initially
be almost symptomless (18). These gliomas, in contrast to the rarer optic nerve
capillaromas and fibromatoses, are characteristically neoplasms of childhood
and are often bilateral. Despite their benign early histologic appearance they
are invasively malignant. A strong family history of neurofibromatosis is present
in most cases, and other intracranial tumors are frequently associated with
them.

The most unusual feature of our cases is the nearly identical character of the
two fourth ventricular subependymal spongioblastomas. Since, in uniovular
twins with a monochorionic, monoamniotic placenta the ectodermal plate is
established before their separation (25), it may be postulated that the site of
neoplasia was determined in the earliest developmental stage of the central
nervous systems of these boys. That individual differences later arose in no
way contradicts this hypothesis. A more rapid growth of the first twin's tumor,
which corresponds to its histologic pattern, would explain the earlier clinical
events. The second twin, who feared he might also have a brain tumor, most
probably had earlier and more severe signs than the history would indicate.
These are but minor variations, however, in an essentially identical develop-
mental history of two fatal tumors.

SUMMARY

The clinical and necropsy reports of monozygous brothers with hydrocephalus
who died at 14 and 16 years of age from similar fourth ventricular spongiobla-
tomas are presented. There was a family history of neurofibromatosis and each
boy had the abortive form of the disease. One twin had macrogenitosomia
praecox, the other had an optic nerve glioma. Previous reports of twins with
neurofibromatosis are reviewed and the unusual features of these new cases dis-
cussed. Since the boys had a monochorionic, monoamniotic placenta, a single
primary defect in their common embryologic ectodermal plate is postulated.

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