DIFFUSE ROSENTHAL FIBER FORMATION IN THE ADULT:
A REPORT OF FOUR CASES

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ABSTRACT

Four cases of unusual formation of Rosenthal fibers widely distributed in the brain stem, spinal cord and paraventricular areas of the brain are described. No clinical neurological syndrome could be attributed to these pathologic changes. The etiology of these changes is not clear but as has been suggested by Herndon et al, they may be related to a congenital or acquired metabolic defect occurring in the astrocytes leading to an abnormal accumulation of glial filaments.

INTRODUCTION

Rosenthal (10) in 1898 described peculiar eosinophilic fibers in the wall of a syringomyelic cavity. These fibers have since been observed in a variety of pathological conditions. Most commonly, they occur as focal phenomena in astrocytomas (4, 5, 12) and in areas of longstanding gliosis. Alexander (1) described their widespread occurrence in the central nervous system in a mentally retarded, hydrocephalic infant. Similar diffuse involvement of the central nervous system has been described in infants (2, 3, 6, 7, 15, 18, 19, 22), in later childhood (10, 21), and in the adult (17). Rosenthal fibers have also been found in and about multiple sclerosis plaques (6, 8). In these cases of diffuse central nervous system involvement the patients had a wide variety of symptoms with evidence of progressive neurological disorder. The present report describes striking and rather widespread distribution of Rosenthal fibers, predominantly in the brain stem and spinal cord, in four patients in whom there was no clinical evidence of a progressive neurological disease referable to the presence of these structures.

CASE REPORTS

Case 1: This 66-year old Caucasian man was hospitalized in 1953, nine years prior to his death because of transient episodes of syncope due to Stokes-Adams' syndrome. He was also found to be diabetic at this time. His symptoms were well-controlled on Ephedrin and a diabetic diet. In 1959, he was hospitalized because of slurred speech and was found to have evidence of a mild dementia and central bulbar paresis which were thought to be related to Stokes-Adams attacks and/or cerebral atherosclerosis. On examination one year

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later, his speech was noted to be slow but not slurred and there were no significant neurological abnormalities. In 1961, he had the acute onset of left hemiplegia thought to be due to thrombosis of the right middle cerebral artery. His last hospitalization in 1962 followed a grand mal convulsion. Neurological examination at that time showed absence of the gag reflex, tongue weakness, slurred speech, impairment of swallowing, a left spastic hemiplegia, left facial weakness and left Babinski sign. It was thought the patient had bilateral cerebral infarcts and pseudobulbar palsy. He died one month after entering the hospital.

**Necropsy findings:** Pathological changes of note in the general organs included bilateral bronchopneumonia, arteriosclerotic heart disease with occlusion of the right circumflex artery, narrowing of the right coronary artery and old infarction of the posterior wall of the right ventricle, colloid adenoma of the thyroid and benign polyp of the large bowel.

**Neuropathological examination** revealed a 5 × 3 cm. area of old ependymomalacia in the right cerebral hemisphere involving the ventral portion of the postcentral gyrus, part of the precentral gyrus and much of the inferior parietal lobule as well as the convolutional and central white matter, insula and putamen. The right lingual gyrus and calcarine cortex were also infarcted and a small area of infarction was noted in the left frontal white matter. The brain stem and cerebellum appeared normal on gross examination. **Microscopic examination** of the cerebral lesions showed the typical changes of old ependymomalacia except that in a few areas, irregular cylindrical, pyiform or spheroidal dense eosinophilic bodies typical of Rosenthal fibers were seen in the subpial region of the preserved molecular layer near the infarct. The most striking changes were seen in the brain stem and in the cerebellum where numerous Rosenthal fibers were scattered in the periaqueductal gray matter, in the walls of the fourth ventricle and in the subpial region in the midbrain, pons and medulla. In the medulla the changes were particularly striking with numerous Rosenthal fibers scattered diffusely throughout the parenchyma in more or less symmetrical fashion. They were particularly numerous in and about the inferior olivary nuclei (Fig. 1A and B), the subpial glial membrane (Fig. 1C), the Obersteiner and Redlich zone of the cranial nerve roots and in the reticular formation. Despite the large numbers of these fibers, the nerve cells appeared normal in morphology (Fig. 1D) and in number and there was no significant increase in glial cells. Occasionally, however, the astrocyte nuclei in these regions were hypertrophied and atypical in appearance. Secondary degeneration was noted in one pyramid of the medulla and was associated with an increase in glia but Rosenthal fibers were less numerous in this tract than in the other preserved tract. In the spinal cord, the Rosenthal fibers were distributed throughout the cervical, thoracic and lumbar segments and were most prominent in the subpial region, in the gray matter and in the posterior columns. The distribution in the corticospinal tracts was again less prominent in that with secondary degeneration than in the preserved tract.

**Case 2:** This 54-year old woman was first admitted to the University of Minnesota Hospitals in 1960, ten days after the excision of a malignant melanoma from the right calf and excision of right inguinal node metastases. Wide local excision of the melanoma site and radical dissection of the popliteal, femoral, inguinal and iliac nodes was carried out, with no evidence of residual tumor or metastases. In 1967, right hilar adenopathy was noted on chest x-ray; this regressed after three courses of intravenous Azotomycin therapy. Two years later, recurrence of hilar adenopathy was treated with Imidazole carbamamide and was followed by a right pneumonectomy. In 1970, she developed rapid mental deterioration, a broad-based gait, motor incoordination, a tendency to fall toward the right and past-pointing to the right. Deep tendon reflexes were hyperactive on the right side and Babinski signs were present bilaterally. The cranial nerve examination was normal. Electroencephalography showed focal abnormalities consistent with left frontal and temporal lobe lesions. She was treated with Decadron, cobalt 60 radiotherapy (3,000 rads to the whole brain) and chemotherapy with some improvement. Her final admission in July, 1979, was because of left lower lobe pneumonia, pleural effusion and leukopenia. She died on the fourth day of hospitalization.

**Necropsy findings:** There was diffuse bronchopneumonia in the left lower lobe with
Fig. 1. (Case 1): Rosenthal fibers diffusely scattered in the medulla, particularly abundant in the inferior olive (A, B) and beneath the pia (C). Nerve cells of the inferior olive are unaltered (D). Hematoxylin and eosin (A, C), azocarmine (B) and Nissl (D) stains; × 120 (A, B, D) and × 300 (C).
organisms resembling Candida. No residual tumor was noted in the lung or in other organs. Neuropathological examination revealed sharply circumscribed cystic necrotic nodules present in the midportion of the right middle frontal gyrus and in the posterior aspect of the left thalamus. These lesions were extensively necrotic and no definite tumor could be identified histologically in them. A cystic necrotic yellow tumor measuring approximately 5 mm. in diameter was found in the posterior lateral aspect of the right cerebellar hemisphere. Microscopic examination of this lesion disclosed an appearance consistent with metastatic melanoma. Although the brain stem was grossly normal, microscopic examination showed numerous Rosenthal fibers scattered symmetrically throughout the parenchyma of the medulla, but more numerous in some areas than others. They were most abundant in the inferior olive (Fig. 2 A, B, C), the medial lemniscus, tectospinal tract, medial longitudinal fasciculus, hilum of the inferior olive (Fig. 2D) and the subpial region. In the caudal portion of the medulla, the fibers were concentrated about the central canal, in the pyramids and reticular substance, in the subpial region, sensory nuclei and tracts and spino-cerebellar tracts. The spinal cord was not available for examination but at the cervico-medullary junction, the Rosenthal fibers were most numerous in the posterior and lateral columns. In the areas where Rosenthal fibers were most abundant occasional astrocyte nuclei appeared hypertrophied (Fig. 2C) but there was no apparent increase in the number of glial cells, nor was there any evidence of neuronal degeneration. Moderate numbers of Rosenthal fibers were present in the periequioductal gray matter and subpial regions of the midbrain and pons and in the colliculi where occasionally there appeared to be a mild increase in glial fibers about small blood vessels. A few widely scattered Rosenthal fibers were found in the roof of the fourth ventricle and in the subependymal region of the third ventricle. No Rosenthal fibers were seen in the areas of metastases either in the cerebrum or in the cerebellum. A portion of the medulla was examined electron microscopically. The tissue was poorly preserved but dense osmiophilic material resembling the appearance of Rosenthal fibers as described by others (6, 12) could be identified. The relationship to the glial fibers could not be established because of postmortem changes.

Case 8: This 19-year old girl was admitted to the University of Minnesota Hospitals in 1970. She had been well until 6 weeks prior to her admission when she developed abdominal pain and cervical and supraclavicular adenopathy. A pathological diagnosis of reticulum cell sarcoma was established on examination of one of the supraclavicular nodes. The tumor was also found in the bone marrow and there was radiographic evidence of involvement of hilar and mesenteric lymph nodes. She received chemotherapy and steroid therapy without significant improvement. During her admission to the hospital, she was examined by a neurosurgeon who found no neurological abnormalities except for somewhat brisk knee and ankle jerks. She received radiotherapy to the abdomen and cervical region and was treated with Vincristine and Cytoxan. Her symptoms improved very briefly but recurred about 10 days later and were accompanied by shooting pains in the buttocks. At this time, neurological examination showed absence of the left ankle jerk and decreased light touch sensation in the fingertips and lateral buttocks areas. She was thought to have a peripheral neuropathy secondary to the Vincristine therapy. Her condition rapidly deteriorated and she died approximately 2 months after the onset of her illness.

Necropsy findings: Significant findings included extensive infiltration of the liver, spleen, axillary lymph nodes, esophagus, duodenum, pancreas, bone marrow and pleura by reticulum cell sarcoma. Broncho-pneumonia was also present. Neuropathological findings included multiple small circumscribed hemorrhages over the surfaces of the cerebrum, brain stem and cerebellum, particularly in the parietal and occipital lobes. These varied from pinpoint to approximately 5 mm. in diameter and appeared to be subpial in location. Similar lesions were scattered throughout the cerebral cortex, thalamus, lateral geniculate bodies, midbrain and pons and in the cerebellum where the lesions were often confluent. A single small discrete hemorrhage was present in the right anterior horn of the L4 segment of the spinal cord. Microscopic examination showed these lesions to be small hemorrhages associated with mi-
Fig. 2. (Case 2): Inferior olive with numerous Rosenthal fibers (A), well preserved nerve fibers (B), and a bizarre astrocyte in the hilum (C). Floor of the fourth ventricle with intact ependyma and scattered Rosenthal fibers in the subependymal region (D). Hematoxylin and eosin stain (A, C, D) and Bielschowsky silver preparation (B); ×120 (A, B) and ×300 (C, D).
nate infiltrates of recticulum cell sarcoma. Tumor emboli were often seen in the blood vessel lumens. Numerous Rosenthal fibers were noted in the sections of the brain stem. These were scattered throughout the tectum and periaqueductal and subpial regions in the midbrain and were occasionally associated with very mild perivascular gliosis. Atypical astrocytes were also seen in this region. Rosenthal fibers were also seen in the wall of the third ventricle near its junction with the aqueduct. In the rostral portion of the pons, the Rosenthal fibers were moderate in number and chiefly in the subependymal and subpial regions. In the rostral medulla, they were scattered throughout the tegmentum but were very sparse in the inferior olives and pyramids. In the upper cervical segments of the spinal cord (Fig. 3), the Rosenthal fibers were numerous in the gray matter about the central canal and in the lateral columns where they were particularly numerous around blood vessels. They were somewhat less numerous in the dorsal gray matter and posterior columns and rare in the anterior horns. Rosenthal fibers were not seen in the thoracic and lumbar segments.

**Case 4:** This 82-year-old Caucasian female was transferred to the University of Minnesota Hospitals in April, 1972 because of the onset of anuria following cholecystectomy. Considerable blood loss was encountered during surgery and the patient became hypotensive. She had a history of hypertension. On admission she was alert and neurological examination was not remarkable. The patient was treated with hydration and diuretics with initial improvement. However, her urinary output remained low and her blood urea nitrogen was elevated. Duodenoscopy was performed and revealed a perforation of the duodenum with massive pneumoperitoneum. During this procedure, the patient had a respiratory arrest and cardiac arrhythmia, from which she recovered. The patient underwent an operation for repair of the duodenal laceration, jejunoctomy and gastrostomy. Following the operation, she was maintained intermittently on a respirator. The day following surgery, she had electrocardiographic evidence of myocardial infarction. She continued to experience symptoms of congestive heart failure, arrhythmia, renal failure and, later in her course, gastrointestinal bleeding. She became comatose terminally but there were no localizing neurological findings. She suffered an episode of bradycardia while being positioned for a lumbar puncture, then became cyanotic and had a cardiac arrest. She died approximately one month following admission.

**Necropsy findings:** Peritonitis, retrohepatic abscess, retroperitoneal abscess, duodenal perforation (repaired), jejunoctomy, gastrostomy, thrombosis of right coronary artery with posterior myocardial infarction, thrombosis of right hepatic artery, nephrosclerosis, and generalized atherosclerosis were the major findings of note in the general organs.

**Neuropathological examination** disclosed no significant external abnormalities in the brain. In sections of the cerebral hemispheres, there was a prominent narrow band of firm, fibrous white tissue in the subependymal region about the terminal vein and extending over the surface of the caudate nucleus, bilaterally. In addition, there was a small focus of infarction in the basis pontis. Microscopic examination showed the subependymal thickenings in the region of the terminal veins to be due to a considerable increase in glial fibers and, to a lesser extent, astrocytes in this region. Numerous Rosenthal fibers were seen scattered throughout this glial tissue particularly about the blood vessels and in the subependymal region (Fig. 4A). In addition to the Rosenthal fibers, there were moderate numbers of corpora amylnac, particularly in the deeper portions of the glial tissue. The astrocytes were often slightly hypertrophied and a few were very large cells with unusually large irregular, hyperchromatic nuclei (Fig. 4B). The bands of glial tissue in which there were numerous Rosenthal fibers extended over the surfaces of the caudate nuclei and terminated just ventral to the terminal vein region. Rosenthal fibers were also seen about the aqueduct, and occasionally in the subpial region of the midbrain. Moderate numbers were also present in the white matter of the roof of the fourth ventricle and in the subependymal portion of the pons. They were not, however, seen in areas of old and recent infarction in the basis pontis. In the medulla, they were sparse in the subependymal region and somewhat more prominent, although not particularly numerous in the subpial region. Sparsely scattered Rosenthal fibers
Fig. 3. (Case 3): Rostral cervical segment of the spinal cord. Abundant Rosenthal fibers distributed symmetrically in the lateral columns and lateral margins of the dorsal columns. The fibers tend to be aggregated about blood vessels and beneath the pia overlying the affected areas. Azocarmine stain; × 10.
were seen in the inferior olivary nuclei chiefly in the hilum and in some of the tegmental nuclei. The spinal cord was not examined.

**DISCUSSION**

The occurrence of widespread Rosenthal fiber formation in the central nervous system has generally been associated with a progressive neurological disor-
nder in infants and young children (1, 2, 3, 6, 7, 16, 18, 19, 22). Vogel and Hallervorden (21) described a progressive neurological illness in a child beginning at approximately the age of seven and progressing for eight years. At autopsy the brain was small with generalized atrophy and numerous Rosenthal fibers were seen diffusely in the brain. A similar case beginning at age 14 and progressing for 12 years was described by Rewcastle (10). In adults, the occurrence of Rosenthal fibers has generally been a focal phenomenon associated with astrocytomas and areas of gliosis such as those occurring about syringomyelic cavities, around the pineal recess and the taenia of the fourth ventricle. Sei et al (17) described a case with a progressive neurological disorder beginning at the age of 32 and progressing for 15 years. This patient's course was characterized by intermittent symptoms including diplopia, slurred speech and left arm paralysis. The slowly progressive course led to a clinical diagnosis of multiple sclerosis. Postmortem examination, however, showed Rosenthal fibers distributed throughout the gray and white matter, especially prominent in the subpial, subependymal and perivascular locations. It was accompanied by a destruction of nerve fibers and myelin with minimal gliosis and little macrophage response. Herndon et al (6) described a 23-year old female (case 3) suffering from anxiety, depression and alcoholism. She had no neurological findings; however, autopsy disclosed focal and extensive Rosenthal fiber formation in the central white matter including the internal capsule where the fibers were concentrated around blood vessels and in the subependymal and subpial region. They were numerous in the anterior medullary velum, in the roof of the fourth ventricle and in the hilum of the dentate nucleus. There was moderate demyelination in the latter. Tihen (20) described the case of a 19-year old man with embryonal carcinoma of the testicle who, at postmortem, was found to have numerous Rosenthal fibers in the periventricular and subpial regions. They were most numerous in the pericanicular area of the upper cervical spinal cord and became progressively more sparse in the more cephalad portions of the brain stem. They were also present in the ventral surface of the hypothalamus, the median eminence, the pituitary stalk, and the optic chiasm. A few were seen in the wall of the third ventricle. The patient also had central pontine myelinolysis.

The four cases reported here were generally similar in character and distribution of the lesions but there were some dissimilarities. For the most part the areas in which Rosenthal fibers were found showed no significant alteration of nerve cell bodies or their axons. Gliosis was generally inconspicuous and usually limited to perivascular areas. An exception to this was noted in case 4 where marked gliosis was noted in the region of the terminal vein in the wall of the lateral ventricle, bilaterally. The areas of Rosenthal fiber formation in the brain stem in this case, however, showed little evidence of gliosis and resembled those in the first three cases. In all of the cases, some of the astrocytes in the involved areas appeared atypical. In most instances this was characterized by mild enlargement, hyperchromatism or irregularity of the nuclei without hyper-
trophy of the cytoplasm. Some astrocytes were unusually large and a few bizarre giant forms were encountered in case 4.

The distribution of the Rosenthal fibers was strikingly similar in the first three cases with a heavy concentration of fibers in the medulla, particularly its more caudal portion. In cases 1 and 3 the spinal cord was also available for examination; in these the Rosenthal fibers appeared to be most numerous in the more cephalad portions. In the pons and midbrain, the Rosenthal fibers were usually limited to the periventricular and subependymal regions in contrast to the medulla where they were scattered more diffusely through the parenchyma. In case 4, the Rosenthal fibers were more prominent in the walls of the lateral ventricle than in the brain stem but the caudal portion of the medulla which seemed more extensively involved in the first three cases was not available for examination in the last case. This apparent difference in distribution may, therefore, be due to sampling.

The two cases cited from the literature (6, 20) and the four cases described in this report appear to constitute a group in which extensive Rosenthal fiber formation occurs in the central nervous system without clinical manifestations. This is apparently due to the fact that, although vital structures are often involved, there is little tissue degeneration. This would seem to indicate that the process is a primary one, perhaps related to some abnormality in the astrocytes, rather than secondary to tissue degeneration and gliosis. This is also supported by the presence of abnormal astrocytes in these areas. These were particularly prominent in cases 2 and 4 where the astrocytes were occasionally very large and bizarre. Some astrocyte nuclei in all cases appeared atypical even when not accompanied by cytoplasmic hypertrophy. In case 4, in addition, the astrocyte processes were often very thick and prominent, particularly about blood vessels. Interspersed among these fibers were typical corpora amylaceae. These laminated bodies have long been recognized in areas of degeneration in the brain and, more commonly, in aged individuals. They are generally most numerous in the subpial, subependymal and perivascular regions of the brain. The relationship of the Rosenthal fibers to corpora amylaceae in the cases reported here is of some interest. The similarities in distribution, i.e. subpial, subependymal and perivascular, of both of these structures is obvious. Electron microscopic studies (6, 9, 13) have shown that both arise within the processes of astrocytes. There are also similarities in ultrastructure. Ramsey described the corpora amylaceae as consisting of a moderately dense matrix bordered by dense linear components with a punctate dense core. The Rosenthal fibers have been found (6) to consist of dense osmiophilic bodies intermingled with dense bundles of glial filaments some of which appeared to enter or course through the dense bodies. Although it is generally accepted that corpora amylaceae increase in number with age and are usually abundant in most aged individuals, this is variable. Corpora amylaceae were identified in all three older individuals in the present study both in areas of Rosenthal fiber formation and in other areas. They were, perhaps, less numerous than might be expected in elderly individuals but this is difficult to
assess. The coexistence of corpora amyacea and Rosenthal fibers may suggest an intermixture of normal and abnormal astrocytes with the normal cells forming corpora amyacea and the atypical ones forming Rosenthal fibers. Until the structure and formation of these bodies is clarified any relationship must remain speculative.

The etiology of these unusual findings is not clear. The occurrence of Rosenthal fibers is probably not age-related since the ages of these patients varies from 19 to 82. In addition, although Rosenthal fibers are occasionally seen in the subpial and subependymal regions of the lower brain stem in older patients, they are usually very sparse even in the very aged. The only common feature which could be found in all of the four cases reported here was the possibility of hypoxia, related to cardiac disease in the first and fourth cases and respiratory distress due to pneumonia and pulmonary tumor involvement in the second and third cases. However, hypoxia alone does not appear to explain the formation of the Rosenthal fibers since Rosenthal fiber formation rarely occurs in old infarcts. This was also true in cases 1 and 4 in which old infarcts were present.

Two of the patients also received cytotoxic agents which have been shown to alter cytoplasmic filaments and microtubules (16) and might also be implicated in two of the cases but not in the others. In addition, Rosenthal fibers have not been described in patients treated with cytotoxic agents.

Herndon et al (6) in a recent review of the pathology of Rosenthal fibers suggested that these fibers may result from a metabolic defect in the astrocyte in pathways responsible for formation or degradation of glial filaments. They have further suggested that in the infantile cases of Alexander's disease, this defect may be present at birth and somehow interfere with the normal nutritional and/or supportive functions of the astrocytes leading secondarily to tissue demyelination or degeneration. In the cases of Alexander's disease of later onset, the metabolic defect is presumed to be latent until some other disease process induces a glial reaction or gliosis in the central nervous system. Such a congenital or acquired metabolic disturbance might also explain the occurrence of the Rosenthal fibers in the present cases but does not satisfactorily explain the topographic distribution unless one assumes that the metabolic defect is a focal or localized one, involving some but not all astrocytes. It is possible that such a defect might be latent until some disturbance in homeostasis, e. g. hypoxia, hypotension or a metabolic disturbance, stimulates a reaction in the astrocyte leading to formation of Rosenthal fibers. An interesting finding in these cases was that tissue degeneration did not appear to stimulate greater Rosenthal fiber formation. This was particularly striking in case 1 where far fewer Rosenthal fibers were found in one pyramid which had undergone secondary degeneration than in the normal pyramid while the distribution was remarkably symmetrical throughout the rest of the medulla. This also suggests that tissue degeneration is not the primary factor in the formation of Rosenthal fibers in these cases. Also unexplained is the occurrence of bizarre astrocytes in some areas of Rosenthal fiber formation while in other areas where Rosenthal fiber formation was often very intense, the astrocytes were relatively normal in
appearance or showed only mild atypism of the nuclei. The findings in these cases of extensive Rosenthal fiber formation with little tissue degeneration perhaps lends some support to the hypothesis that in Alexander's disease the primary abnormality is in the astrocytes and that the neuronal degeneration is secondary. The question of the relationship of the cases presently described to the typical Alexander's disease with progressive neurological degeneration should also be considered. These cases might represent a forme fruste of Alexander's disease but until the etiology of these entities is better defined they probably should be classified separately.

REFERENCES