Papilledema in Patients with Severe Pulmonary Emphysema*

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Abnormalities of function of the central nervous system that occur in association with severe pulmonary emphysema have been reported with increasing frequency. This trend may represent an increase in the actual incidence of severe emphysema but it also may reflect a better understanding of mechanisms involved and consequently a greater index of awareness by clinical observers. The paradoxical manifestations of both depression and irritability of the central nervous system have been attributed to hypoxia, hypercapnia, polycythemia, cor pulmonale and alterations in cerebral blood flow with associated increase in cerebrospinal fluid pressure.

A small portion of these patients manifesting one or more of the features of headache, mental cloudiness and muscular twitching in addition to signs of pulmonary insufficiency may be found to have varying degrees of papilledema.†† Sieker and Hickam reported that one patient in their series of 25 patients with classic carbon dioxide intoxication complicating severe chronic pulmonary insufficiency had papilledema. Numerous others have described the finding of papilledema in such patients which usually led to detailed investigation of the central nervous system to eliminate the possibility of an expanding intracranial lesion. The patient's altered sensorium often thwarted the physician's efforts to elicit the cause of the papilledema and necessitated the accumulation of objective evidence to exclude the presence of a brain tumor.

The purpose of this paper is to add to the small but growing number of cases which have been reported and to gain additional information about the clinical ramifications of this problem.

Report of Cases

Case 1: A 52-year-old machinist registered at the Mayo Clinic on August 9, 1957, complaining of shortness of breath for 2 years, first noted when he tried pushing his car in cold weather. For many years prior to this he had had cough in the morning with expectoration of 1 ounce of yellow to gray sputum. He had smoked one package of cigarettes daily for many years. Waves of nausea had troubled him at times during meals but there had been no vomiting and no heartburn. To aid in breathing he had taken pills which also made him sleepy. For about 2 weeks prior to his registration he had been taking cortisone. Dyspnea had progressed so that he was out of breath after walking one block at a normal pace. He denied having thoracic pain.

On physical examination he weighed 137 pounds and his height was 5 feet, 3½ inches. His blood pressure measured 170 mm. of mercury systolic and 105 mm. diastolic, the pulse being 88 and regular. The anteroposterior diameter of the chest appeared greater than normal and breath sounds were generally diminished. The edge of the liver was palpable and sharp three fingerbreadths below the right costal margin. No spider angiomata were noted.

Urinalysis showed albumin, grade 2. The hemoglobin measured 15.4 gm. per 100 cc., the erythrocytes numbered 5,380,000 and the leukocytes, 7100 per cubic millimeter of blood. The sedimentation rate was 15 mm. in 1 hour by the Westergren method. The urea measured 28 mg. per 100 cc. of whole blood. The serum bilirubin was nega-

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tive direct and 0.25 mg. indirect. The Kline flocculation test for syphilis was nonreactive. A bromsulphalein test for function of the liver showed 8 per cent retention in 1 hour. A roentgenogram of the thorax showed evidence of a Ghon complex and decreased peripheral markings suggesting emphysema (fig. 1). Roentgenograms of the gallbladder, esophagus, stomach, duodenum and colon were without evidence of abnormality except for moderate diverticulosis of the colon. No evidence of abnormality was apparent on roentgenograms of the sinuses and the skull. Examination of the optic fundi revealed bilateral papilledema of 1 1/2 to 2 diopters. Only mild hypertensive arteriolar changes were noted and there was no peripheral retinopathy. The visual fields were normal. The electrocardiogram showed large P waves in leads I and II as often seen in cases of emphysema (fig. 2).

The results of neurologic examination were objectively normal except for the papilledema. Tests of pulmonary function indicating the presence of severe emphysema are shown in the table. Bilateral carotid angiograms and a ventriculogram were interpreted as being normal.

The hematocrit reading was 56 per cent on one occasion and 60 per cent 4 days later. The volume of whole blood was 81 cc. per kilogram of body weight and the plasma volume was 33 cc. per kilogram. Clinically the hemalogic picture appeared to be that of mild secondary relative polycythemia associated with chronic pulmonary insufficiency.

The patient stopped smoking, practiced breathing exercises regularly and noted remarkable relief of his dyspnea and chronic productive cough. Penicillin was administered for 6 days because of the somewhat purulent appearance of the sputum, and this more than likely contributed measurably to his improvement. This moderate degree of improvement has been maintained with temporary recurrence of symptoms during even mild acute respiratory infections.

Case 2: A 53-year-old highway construction worker registered on December 14, 1955, because of shortness of breath of 6 months' duration, insidious in onset and gradually progressive without orthopnea. He also had noted some substernal pressure on exertion with prompt subsidence on resting. He had cough but no hemoptysis.

Physical examination showed dyspnea from the exertion of undressing. Oral hygiene was poor. Maximal expansion of the thorax was only half an inch, with normal resonance but distant breath sounds and prolonged expiration. Inspiratory crackling rales were noted in the bases of both lungs. The liver, spleen and superficial lymph nodes were not enlarged. Bilateral pedal edema was moderately severe. Ophthalmoscopic examination showed moderate bilateral papilledema and venous engorgement. The results of neurologic examination were normal. The venous pressure in the right arm was 18 cm. of water.

Urinalysis showed slight microhematuria. The hemoglobin measured 13.5 gm. per 100 cc. Erythrocytes numbered 4,310,000 and leukocytes 5600 per cubic millimeter of blood. The sedimentation rate was 2 mm. in 1 hour by the Westergren method. Urea measured 16 mg. and sugar 94 mg. per 100 cc. of blood. The bilirubin was negative direct and 0.72 indirect. Further studies of the blood showed the following values: chlorides 99.4 mEq. and carbon dioxide combining power 26 mEq. per liter.
of plasma; albumin 3.49 gm. and globulin 1.6 gm. per 100 cc. of serum. No retention was present 1 hour after the bromsulphalein test for hepatic function. The Kline serologic test for syphilis was nonreactive. The hematocrit reading was 52 per cent on one occasion and 63 per cent 3 days later. An excretory urogram showed nephroli-thiasis on the left. Results of studies of pulmonary function are shown in the table. Calcium measured 10.8 mg. per 100 cc. of serum and phosphate 4.2 mEq. per liter of serum. Similar values were found when these tests were repeated the next day. A roentgenogram of the thorax (fig. 3) showed evidence of advanced emphysema and considerable enlargement of the heart. The electrocardiogram showed evidence of right ventricular hypertrophy (fig. 4).

Treatment with digoxin, aminophylline, mercaptoperin (thiomerin) and penicillin as well as isuprel aerosol resulted in diuresis so that the patient lost 25 pounds with clearing of the edema and considerable improvement in dyspnea. Phlebotomy of 500 cc. of blood was carried out on two occasions. Little change in the papilledema was observed during the 10 days of treatment. He was dismissed to go home, with advice to continue with treatment and to restrict his activities.

Case 3: A 38-year-old farm wife who had had asthma all her life registered in the Section of Ophthalmology because of progressive blurring of vision of several months' duration. She had been seen at the clinic on numerous previous occasions for chronic recurrent and protracted asthma as well as during several pregnancies. Acute papilledema was noted bilaterally and varied from 2 to 3+ diopters. Plotting of the visual fields showed an enlarged blind spot on the right resulting from the papilledema. The precise mapping of the left blind spot was inaccurate because of long-standing amblyopia which prevented adequate fixation. Eclampsia of pregnancy had led to fetal death in four of her seven deliveries. There had been no convulsions at other times.

On numerous examinations at the clinic her blood pressure was never greatly elevated, the highest reading being 144 mm. of mercury systolic and 96 mm. diastolic during her sixth pregnancy. Recent colds had been prolonged and associated with advanced dyspnea and wheezing (fig. 5). Activities had been almost eliminated during these respiratory infections.

Physical examination revealed dusky cyanosis of the face and fingernail beds and some impairment of sensorium. There were bilateral inspiratory rhonchi with depression of breath sounds especially on the left. The expiratory phase of respiration was longer than the inspiratory phase. She had bilateral varicose veins and pretibial edema of moderate degree. She weighed 134 pounds which was about 8 pounds more than her usual weight, and her height was 5 feet. The blood pressure measured 112 mm. of mercury systolic and 80 mm. diastolic, the pulse being 108 and regular. Neurologic examination gave essentially normal results.

**FIGURE 3**

*Posteroanterior view of the thorax (case 2); showing diffuse advanced emphysema and considerable cardiac enlargement.*

**FIGURE 4**

*Electrocardiogram showing evidence of right ventricular hypertrophy (case 2).*
### RESULTS OF STUDIES OF PULMONARY FUNCTION

<table>
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<th>Cases 1</th>
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<th>Cases 3</th>
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<tr>
<td>Breathing (1 min.) (5 min.) (1.6 min.)</td>
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*After inhalation of 1 cc. of nebulized arterenol (1:400). †Trapping present. ‡Concentration of alveolar nitrogen after breathing 100% oxygen for 2 minutes.

Urine analysis showed a few leukocytes and erythrocytes microscopically, the specific gravity being 1.012. The hemoglobin measured 16.4 gm. per 100 cc. of blood; the erythrocytes numbered 5,000,000 and the leukocytes 6600 per cubic millimeter. The sedimentation rate was 3 mm. in 1 hour by the Westergren method. The hematocrit reading was 62 per cent. A blood smear did not show cellular immaturity. Roentgenograms of the thorax showed evidence of bilateral apical pleural thickening, adhesions at both costophrenic angles and fibrotic regions in the base of the left lung. A roentgenogram of the skull did not show any evidence of abnormality. The results of tests of pulmonary function are shown in the table.

Phlebotomy was performed three times and the hematocrit reading subsequently was found to be 55 per cent. When spinal fluid examination was done it was traumatic. The results of erythrocyte and leukocyte counts were not considered to be of

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![FIGURE 5: Posteroanterior view of the thorax (case 3) showing diffuse increase in pulmonary markings particularly in the bases which suggest the presence of bronchiectasis and fibrosis complicating long-standing asthma and emphysema.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21337/)
diagnostic value. Spinal fluid protein measured 45 mg. per 100 cc. and the values for sugar and chlorides also were normal. A ventriculogram was normal.

A program of isuprel aerosol four times daily for 15 minutes was started and oxygen was used frequently while the patient was under observation. Periodic antibiotic therapy was advised for bronchial infection.

Only the severe improvement from the previous pulmonary insufficiency seemed to result and each respiratory infection was followed by a severer and longer attack. In February, 1957, the patient died, 2 years after her last examination at the clinic. Necropsy revealed chronic bronchitis and bronchiectasis, emphysema and advanced cerebral edema with generalized flattening of the generalization of the hippocampal gyrus and notching of the pes pedunculi on the left. The tonsils of the cerebellum were herniated and the brain stem was distorted. Cut sections did not show focal lesions.

Comment

Several factors apparently may contribute to papilledema occurring in patients with chronic pulmonary insufficiency. Polycythemia of the primary type or secondary pulmonary insufficiency with increased total blood volume may contribute to papilledema. Whether hypoxia alone or through stimulation of polycythemia contributes to papilledema is not certain. Austen and associates, in reporting on four pulmonary cripples with neurologic abnormalities, three of whom had papilledema, commented that this funduscopic finding is not seen in patients with congenital cyanotic heart disease. We have not seen papilledema in patients with diffuse interstitial fibrosis characterized by hypoxemia but with no impairment of intrapulmonary mixing of gases. We have seen papilledema in two patients with the syndrome of obesity, hypoventilation and polycythemia. The physiology of the obese patients resemble those in our three cases reported herein. Thus retention of carbon dioxide seems to be an important factor in the genesis of papilledema.

Tests of pulmonary function showed rather advanced arterial hypoxemia in all three of our patients at rest and especially during exercise. In addition, however, relative polycythemia was demonstrated by the hematocrit reading or the hemoglobin determination or both. There was no clinical or laboratory evidence of polycythemia vera. Studies of lung volumes in the two men showed the characteristics of emphysema. The woman, who suffered repeated respiratory infections, but also notable characteristic of combined fibrosis and emphysema. These findings were supported by the small total lung capacity and by necropsy showing diffuse moderate bronchiectasis with peribronchial fibrosis.

Crucial features of pulmonary insufficiency associated with papilledema have been abnormally uneven intrapulmonary mixing of gases leading to retention of carbon dioxide and respiratory acidosis. Although frank alterations in carbon dioxide combining power were not always demonstrated at the time of the laboratory studies in our cases, grossly abnormal nitrogen washout patterns while the patients were breathing 100 per cent oxygen indicated that the stage was set for such complications. The frequent occurrence of hypoxia, polycythemia, signs of pulmonary hypertension and frank congestive failure further implicated retention of carbon dioxide as a causative factor since all of these abnormalities frequently coexist. Recent studies show that local blood flow in cerebral blood flow with concentrations of carbon dioxide (5 to 7 per cent) lend support to the important role of high partial pressure of carbon dioxide in the blood in this syndrome. Furthermore, Simpson and Davies and Mackinnon demonstrated increased cerebrospinal fluid pressure as their subjects breathed gas mixtures containing high concentrations of carbon dioxide. Simpson described herniation of the cerebellar tonsils into the foramen magnum found at necropsy in patients with pulmonary insufficiency and papilledema. Necropsy in the one fatal case in our series showed general cerebral edema as well.

Therapy with aerosol bronchodilators, appropriate antibiotics and mechanical assistants directed at improving ventilation with adequate elimination of carbon dioxide and oxygenation of the blood may bring about temporary and sometimes prolonged clinical improvement. The appearance of this syndrome, however, is usually an ominous sign prognostically.

SUMMARY

Papilledema in association with severe pulmonary insufficiency has been uncommon until recently when it has been reported with increased frequency. Common features of reported cases, including three from the Mayo Clinic, have included emphysematous pulmonary changes alone or associated with chronic asthma, bronchitis, or fibrosis. Impaired intrapulmonary mixing of gases has been of such severe degree as to lead to both hypoxia and retention of carbon dioxide. Frequently polycythemia, cor pulmonale and congestive failure also have been present. Neurologic manifestations have included altered sensorium, confusion, headache, weakness, blurred vision, muscular twitching and, occasionally, coma complicating respiratory infection, pharmacologic depression of respiration or therapy with high tensions of oxygen. Papilledema is apparently one of the most extreme and unusual signs of the adverse effects of severe pulmonary insufficiency on the central nervous system.
RESUMEN
El papilemiento con insuficiencia pulmonar grave no ha sido común hasta recientemente, que ha sido relatado con frecuencia creciente. Las características de los casos relatados, incluyendo tres de la Clínica Mayo, incluyen: trastornos pulmonares enfisematosos, solos o asociados con asma crónico, bronquitis o fibrosis. La mezcla de gases defectiva dentro del pulmón, ha sido tan severa que ha conducido a hipoxia y retención de dióxido de carbono. También se encuentran frecuentemente policitemia, cor pulmonale y la insuficiencia congestiva. Las manifestaciones neurologicas han incluido trastornos sensoriales, confusión, cefalalgia, debilidad, visión borrosa, contracciones musculares o ocasionales como ceguera, disconciencia, depresión psicomotorria de la respiración o con el tratamiento de oxígeno a alta presión. El papilemiento es aparentemente uno de los más extremos signos de los efectos adversos de la insuficiencia pulmonar grave sobre el sistema nervioso central.

Referencias