A REVIEW OF FACTORS IN THE PATHOGENESIS OF PSEUDOTUMOR CEREBRI

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Clinicians apply the term cerebral pseudotumor to a clinical syndrome of diverse etiologies. Benign intracranial hypertension, a synonym suggested by Foley,[1] describes a condition characterized by an undistorted ventricular system of normal size in the presence of increased intracranial pressure. In practice the diagnosis of pseudotumor requires pneumographic visualization of the ventricular system. Three conditions can produce increased intracranial pressure without either distortion or enlargement of the cerebral ventricles : 1.) obstruction of venous outflow from the skull; 2.) active cerebral vasodilation, arteriolar rather than venous; and 3.) cerebral edema.

A major deterrent in the consideration of pathogenesis is a paucity of pathologic information. An increase in the intracranial vascular compartment cannot be determined during life or after death even with our present highly refined methods. Although available evidence indicates that cerebral edema accounts for the majority of cases fulfilling rigid diagnostic criteria for pseudotumor, to consider pseudotumor tantamount to cerebral edema is to substitute lack of information for ignorance, and to accept cerebral edema as one cause of benign intracranial hypertension adds nothing to an understanding of the problem. For example, present evidence does not allow distinction of generalized brain edema involving gray and white matter from edema confined to white matter alone, either by an increase in the true extracellular space or by accumulation of intralamellar fluid within the myelin sheath. The light microscopic study of cortical biopsies reported by Sahs and Joynt revealed interstitial and intracellular edema involving gray and white matter, but the validity of their observations must be seriously questioned in view of present knowledge concerning the vagaries of light microscopy.[2] Presumably the edema of pseudotumor involves an increase in water and sodium content, but precise information is lacking. In

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all probability the edema of pseudotumor is subtle because cerebral function remains undisturbed.

The Monro-Kellie hypothesis considers the skull as a rigid box open to the atmosphere only through the vascular system and containing : 1.) incompressible brain; 2.) a compressible vascular system; 3.) cerebrospinal fluid, a compartment which is incompressible, but which can be reduced or increased within a matter of minutes.

Foley[1] classified pseudotumor into three categories : 1.) postotitic; 2.) following non-otitic infections or mild head injury; and 3.) those cases without a history of infection or head injury and among which he considered endocrine factors paramount. We have reviewed the relevant literature attempting to reduce a large body of information into a coherent etiologic classification of the diverse causes of the pseudotumor syndrome (Table 1). We have omitted intracranial hypertension due to vascular hypertension and due to recognized, although imperfectly understood, causes of

TABLE 1

CAUSES OF BRAIN SWELLING

1. Endocrine Factors
   a. adrenal cortical insufficiency.
   b. ovarian dysfunction
   c. hyperpituitarism
   d. hypoparathyroidism
   e. hormonal imbalance
2. Drugs
   a. steroid therapy of withdrawal
   b. contraceptives
   c. antibiotics
   d. vitamin A
3. Venous Obstruction
   a. intracranial
   b. extracranial
4. Post-traumatic
5. Post-infectious
   a. otitic
   b. non-otitic
6. Miscellaneous
   a. hypercapnia
   b. anemia, polycythemia
   c. alkalosis
7. Idiopathic

cerebral edema such as lead poisoning. We have included uncommon and often unrecognized causes of intracranial hypertension and will elaborate on pathogenic factors which have attracted primary attention in the past.

Many authors have considered endocrine factors in cases of pseudotumor without obvious cause. Although adrenal insufficiency [3] may be accompanied by increased intracranial pressure and cerebral edema, the characteristic signs and symptoms of Addison's disease, even in mild form, are conspicuously absent in the patient with idiopathic pseudotumor. A relative adrenocortical or pituitary hypofunction may be precipitated in patients on long term steroid therapy consequent to a relative increase in steroid requirements, for example, by infections or by a reduction in dosage. While adrenocortical insufficiency and related cerebral edema respond promptly to adequate doses of steroid, the response is in no way specific.

Abnormal estrogen metabolism has been implicated in the genesis of idiopathic pseudotumor because of the predominance of females in the idiopathic group, and among them the common findings of obesity, hirsutism, pregnancy, menstrual disorders and miscarriage. Greer's studies of pseudotumor related to pregnancy,[4] menarche [5] and menstrual dysfunction lend supporting evidence for the estrogenic theory. Smooth muscle relaxes in the last few days of the menstrual cycle and during pregnancy, and the smooth muscle of arterioles shares this relaxation. Diffuse cerebral arteriolar dilatation could easily produce enlargement of the vascular bed sufficient to cause intracranial hypertension. Secondarily, arteriolar dilatation could lead to transudation of water into the extracellular space. Circumstantial evidence favoring disordered estrogen metabolism has received little support from studies of endocrine function, and, to our knowledge, hormone therapy, with the exception of adrenal cortical steroids, has not been employed successfully in the treatment of pseudotumor. In Paterson's [6] carefully documented study, the majority of patients were women in the reproductive age, one half with menstrual irregularity or pregnancy and obesity, and three non-pregnant patients with galactorrhea. She suggested that the endocrine disorder was one of functional or physiologic hyperpituitarism. This concept could apply to pregnancy, Addison's disease, simple obesity, ammenorrhea and following reduction of steroid dosage after long term use.

Hypoparathyroidism may be accompanied by papilledema secondary to cerebral edema.[7] Air studies in reported cases have shown

ventricles of normal or small size. In contrast to the healthy state of patients with pseudotumor, papilledema in patients with hypoparathyroidism has been accompanied by signs and symptoms of the disorder and invariably has been associated with hypocalcemia, giving little substance to the possibility that occult hypoparathyroidism plays any significant role in the idiopathic pseudotumor syndrome. In discussion of etiology, several authors have proposed endocrine factors or hormone imbalance,[8, 9] but these unsupported statements have added nothing to our understanding of pseudotumor.

Benign intracranial hypertension due to cerebral edema has been reported in patients receiving long term adrenal corticosteroid therapy.[10, 11, 12, 13, 14, 15] In all reported cases steroids have been administered for at least five months and the majority of patients were under ten years of age. The typical patient has been a child receiving long term steroids for asthma, eczema or rheumatoid arthritis. In practically all cases the syndrome developed as steroid therapy was modified by a decrease in quantity or a change to another compound. Most authors have concluded that the underlying basis for cerebral edema was suppression of adrenal activity, directly or medicated through suppression of ACTH production. Cerebral edema has responded promptly to the reinstitution of previous steroid therapy.

The occurrence of the pseudotumor syndrome in females receiving oral contraceptive agents gives additional support to the role of endocrine factors. All of the four patients reported by Walsh [16] had papilledema and increased intracranial pressure and all recovered after withdrawal of contraceptive drugs. These patients had pseudotumor by clinical and radiographic criteria.

Increased intracranial pressure has been reported in infants following administration of tetracycline, oxytetracycline and chlortetracycline.[17, 18, 19, 20] Signs and symptoms can develop within hours following institution of therapy, and in all cases signs and symptoms have disappeared when the drug was discontinued. The prompt appearance and disappearance of intracranial hypertension is consistent with cerebral edema although proof is lacking. Use of the terms toxic and allergic hardly veils our ignorance of causative mechanisms.

Vitamin A poisoning [21, 22, 23, 24, 25] has been described as a cause of acute intrancranial hypertension in infants and also in adolescents

taking large doses of vitamin A for acne. In infants, ingestion of 350,000 units of vitamin A leads to an acute disturbance which begins about 12 hours following ingestion and subsides without treatment. Experimentally, vitamin A intoxication causes cerebral edema, but in one reported case studied by ventriculography the ventricles were slightly dilated.

Obstruction of the dural venous sinuses unrelated to ear infection has received considerable attention because of the recognized relationship between otitic infections and lateral sinus thrombosis.[26] The relationship between venous sinus occlusion[27] and increased intracranial pressure is complicated by evidence indicating that the ventricular system may be small, normal or dilated. Thrombosis of the dominant lateral sinus, usually the right, has been documented by angiographic and postmortem studies. Non-otitic causes of obstruction have included primary[28] and metastatic tumors,[29] trauma[30] and apparently spontaneous thrombosis, and the increased intracranial pressure has been considered primarily related to interference with venous drainage and only questionably related to reduced absorption of cerebrospinal fluid. Occlusion of a major venous sinus does not always lead to increased intracranial pressure as shown by clinical reports and experimental studies.[31] In a great majority of instances intracranial hypertension due to venous sinous obstruction has been associated with either small or normal ventricles, and the basis of intracranial hypertension has presumably been enlargement of the vascular bed or cerebral edema.[32, 33] Kinal's report[34] of hydrocephalus secondary to congenital atresia or stenosis of the dural venous sinuses must be questioned although clinical and experimental studies have shown a relationship between sagittal sinus hypertension and infantile hydrocephalus. The original report of Ray and Dunbar[35] suggested that thrombosis of the dural venous sinuses was a frequent cause of pseudotumor. Additional experience has shown that venous sinus occlusion accounts for relatively few cases.

Increased intracranial pressure may follow unilateral radical neck dissection[36] if the operation is performed on the side of a dominant lateral sinus, and intracranial hypertension of some degree almost always follows simulataneous bilateral radical neck dissection.[37] Post mortem and clinical evidence suggests that in many cases the mechanism is a generalized cerebral edema upon which is superimposed expansion of the venous bed. Without proof, some authors have suggested that impairment of cerebrospinal fluid

absorption leads to a state of hyrocephalus rather than cerebral edema. An exception was Hooper's patient who developed communicating hydrocephalus secondary to obstruction of the superior vena cava.[38] Bering [30] has provided additional evidence that increased cephalic pressure can lead to hydrocephalus.

A benign form of increased intracranial pressure has been reported to follow minor head injury,[10, 41, 42, 43] but the relationship is unclear. In few reported cases have subdural fluid collections in the form of hydromas or hygromas been excluded by appropriate studies. A review of the literature provides little information on the occurrence of fully documented cases, and as a cause of the pseudotumor syndrome mild head injury must be uncommon.

The occurrence of pseudotumor following infection of the middle ear and mastcid has been confirmed by abundant clinical, surgical, radiographic and postmortem evidence.[22, 8, 44] Among 224 cases of pseudotumor reviewed by Millichap,[43] 37 per cent were children. Two thirds of all cases following otitis media occurred in children, a freşuency reflecting the age distribution of ear infection. In anatomically documented cases of otitic pseudotumor, thrombosis has involved the dominant lateral sinus, with or without extension to and beyond the torcular Herophili. Although venous hypertension may impair absorption of cerebrospinal fluid to some degree, expansion of the venous bed and cerebral edema predominate, giving rise to increased intracranial pressure in the presence of small or normal ventricles. The relationship between otitic infections and increased intracranial pressure cannot be explained on the basis of lateral sinal thrombosis in all cases and, furthermore, non-otitic infections have been implicated as a cause of the pseudotumor syndrome. Although all available evidence supports a reasonably good correlation between post-otitic pseudotumor and lateral sinus thrombosis, the correlation is *not* perfect and additional factors must be found to explain the remaining post-otitic and other post-infectious cases.

Increased intracranial pressure is a recognized complication of inadequate pulmonary ventilation.[15, 16, 17] The underlying basis appears to be hypercapnia with hypoxemia and venous hypertension playing minor or secondary roles. Hypercapnia produces vasodilatation which is probably associated with varying degrees of cerebral edema. Hypoventilation with hypercapnia explains the occurrence of papilledema and pseudotumor following bulbar poliomyelitis.[18]

Unrecognized hypercapnia as a cause of pseudotumor in healthy persons can be dismissed.

Severe anemia, and particularly iron deficiency[49] anemia,[50] may be associated with intracranial hypertension. The increased intracranial pressure appears to be secondary to cerebral edema resulting from capillary and tissue anoxia. The cause of papilledema in polycythemia vera is not entirely clear, but may be related to cerebral vasodilatation and secondary stagnant hypoxia. Alkalosis, if severe and prolonged, may produce increased intracranial pressure by complex mechanisms. The occurrence of papilledema in other biochemical disorders can be explained on the basis of hypercapnia, and other electrolyte disturbances and wide deviations from normal osmolarity can lead to cerebral edema as typified by the condition of water intoxication.

Much has been said about the minority of cases of pseudotumor and, now confronted with the majority of cases, we must apologize for our ignorance. Circumstantial evidence implicates endocrine factors, but evidence favoring this theory has been clinical and meager. Drug-related cerebral edema is important only in providing information which may illuminate causes in the much larger number of unexplained cases. Post-otitic pseudotumor falls into a neat category, but with the advent of antibiotics this group will diminish in importance. In the final analysis the pathogenesis of the large majority of cases remains unknown.[31, 14, 52, 2] The most promising field for clinical research appears to be endocrinology. Biochemical and ultrastructural studies of biopsy material may provide critical information, but successful medical management allows few opportunities for obtaining surgical biopsies. We suggest that all patients with pseudotumor be studied exhaustively from the endocrine standpoint, and that attention be turned to immunologic mechanisms of brain swelling. Progress made in the past half century leaves little room for optimism.

Summary

Pseudotumor cerebri may be caused by a number of recognized mechanisms, but in the majority of instances etiology is not determined. Known causes of brain swelling are reviewed, and various theories regarding the pathogenesis of idiopathic pseudotumor are discussed. Considerable evidence implicates subtle and perhaps varied endocrine dysfunction as the basis for at least some cases of pseudotumor presently termed idiopathic.

REFERENCES

1. Foley, J.: Physiology of increased intracranial pressure, in Modern Trends of Neurology, New York, ed. Williams and Hober, 1957, p. 49.
2. Sahs, A. L. and Joynt, R. J.: Brain swelling of unknown cause, Neurology 6: 791, 1956.
3. Jefferson, A.: Clinical correlation between encephalopathy and papilloedema in Addison's disease, J. Neurol. Neurosurg. & Psychiat. 19: 21, 1956.
4. Greer, M.: Benign intracranial hypertension. III, Pregnancy, Neurology 13: 670, 1963.
5. Greer, M.: Benign intracranial hypertension. IV, Menarche, Neurology 14: 569, 1964.
6. Paterson, R., Depasquale, N. and Mann, S.: Pseudotumor cerebri, Medicine (Balt) 40: 85, 1961.
7. Sugar, O.: Central neurological complications of hypoparathyroidism, A. M. A. Arch. Neurol. Psychiat. 70: 86, 1953.
8. Foley, J.: Benign forms of intracranial hypertension - «toxic» and «otitic» hydrocephalus, Brain 78: 1, 1955.
9. Jacobson, H. G. and Shapiro, J. H.: Pseudotumor cerebri, Radiology 82: 202, 1964.
10. Benson, P. F. and MacKeith, R. C.: Pseudotumor cerebri, Lancet 2: 55, 1961.
11. Dees, S. C. and McKay, H. W.: Occurrence of pseudotumor cerebri (benign intracranial hypertension) during treatment of children with asthma by adrenal steroids, Pediatrics 23: 1143, 1959.
12. Greer, M.: Benign intracranial hypertension. II, Following corticosteroid therapy, Neurology 13: 439, 1963.
13. ———: Intracranial hypertension and steroids, Lancet 2: 1052, 1964.
14. Maisel, J. E. and Caplan, J.: Pseudotumor cerebri benign intracranial hypertension, J. Pediat. 52: 441, 1958.
15. Walker, A. E. and Adamkiewicz, J. J.: Pseudotumor cerebri associated with prolonged corticosteroid therapy. Reports of four cases, J. A. M. A. 188: 779, 1964.
16. Walsh, F. B., Clark, D. B., Thompson, R. S. and Nicholson, D. M.: Oral contraceptives and neuro-ophthalmologic interest, Arch. Ophthalmology 74: 628, 1965.
17. Fields, J. P.: Bulging fontanel: a complication of tetracycline therapy in infants, J. Pediat. 58: 74, 1961.
18. Gellis, S.: Editorial comment in Year Book of Pediatrics, Chicago, Year Book Publishers, 1956, p. 40.
19. Koch-weser, J. and Gilmore, E. B.: Benign intracranial hypertension in an adult after tetracycline therapy, J. A. M. A. 200: 345, 1967.
20. O'Doherty, N. J.: Acute benign intracranial hypertension in an infant receiving tetracycline, Develop. Med. Child. Neurol. 7: 677, 1965.
21. Bass, M. H. and Caplan, J.: Vitamin A deficiency in infancy, J. Pediat. 47: 690, 1955.

22. Davidoff, L. M. and Dyke, C. G.: Hypertensive meningeal hydrops: Syndrome frequently following infection in middle ear or elsewhere in the body, Amer. J. Ophthal. 20: 908, 1937.
23. Ford, F. R.: Diseases of the nervous system in infancy, in Childhood and Adolescence, Springfield, Charles C. Thomas, ed. 4, 1960.
24. Gribetz, D., Silverman, S. H. and Sobel, A. E.: Vitamin A poisoning, Pediatrics 7: 372, 1951.
25. Marie, J. and See, G.: Acute hypervitaminosis A of infant; its clinical manifestations with benign acute hydrocephalus and pronounced bulge of fontanel; clinical and biologic study, A. M. A. Am. J. Dis. Child. 87: 731, 1954.
26. Reading, P. V. and Schurr, P. H.: Thrombosis of the sigmoid sinus; past and present, Lancet 2: 473, 1956.
27. Friedman, M. W.: Bilateral papilledema in otherwise well patients, Arch. Ophth. 58: 59, 1957.
28. Marr, W. G. and Chambers, J. W.: Occlusion of the cerebral dural sinuses by tumor simulating pseudotumor cerebri, Amer. J. Ophthal. 61: 45, 1966.
29. Mones, R. J.: Increased intracranial pressure due to metastatic disease of venous sinuses. A report of six cases, Neurology 15: 1000, 1965.
30. Meirowsky, A. M.: Wounds of dural sinuses, J. Neurosurg. 10: 495, 1953.
31. Owens, G., Stahlman, G., Capps, J. M. and Meirowsky, A. M.: Experimental occlusion of dural sinuses, Surg. Forum 8: 521, 1957.
32. Jaeger, R.: Symposium: intracranial vascular abnormalities; observations on resection of superior longitudinal sinus at and posterior to rolandic venous inflow, J. Neurosurg. 8: 103, 1951.
33. Kinal, M. E.: First International Congress of Neurological Sciences, ed. by Von Bogart and Rodermecker, Vol. 2, 1957, p. 178.
34. Kinal, M. E.: Hydrocephalus and the dural venous sinuses, J. Neurosurg. 19: 195, 1962.
35. Ray, B. S. and Dunbar, H. S.: Thrombosis of dural venous sinuses as a cause of «pseudotumor cerebri», Ann. Surg. 134: 376, 1951.
36. Marr, W. G. and Chambers, R. G.: Pseudotumor cerebri syndrome following unilateral neck dissection, Amer. J. Ophthal. 51: 605, 1961.
37. Rosenfeld, L. and Jacobs, J. K.: Bilateral radical neck dissection, Surgery 49: 359, 1961.
38. Hooper, R.: Hydrocephalus and obstruction of the superior vena cava in infancy. Clinical study of the relationship between cerebrospinal fluid pressure and venous pressure, Pediatrics 28: 792, 1961.
39. Bering, E. A. and Salibi, B.: Production of hydrocephalus by increased cephalic venous pressure, Arch. Neurol. Psychiat. 81: 693, 1959.
40. Beller, A. J.: Benign post-traumatic intracranial hypertension, J. Neurol. Neurosurg. & Psychiat. 27: 149, 1964.
41. Feigin, I. and Popoff, N.: Neuropathological changes late in cerebral edema: The relationship to trauma, hypertensive disease and Binswanger's encephalopathy, J. Neuropath. & Exper. Neurol. 22: 500, 1963.

42. French, L. A. and Galicich, J. H.: The use of steroids for control of cerebral edema, Clin. Neurosurg. 10: 212, 1964.

43. Millichap, J. G.: Benign intracranial hypertension and otitic hydrocephalus, Pediatrics 23: 257, 1959.

44. Kinal, M. E. and Jaeger, R. M.: Thrombophlebitis of dural venous sinuses following otitis media, J. Neurosurg. 17: 81, 1960.

45. Freedman, B. J.: Papilloedema, optic atrophy and blindness due to emphysema and chronic bronchitis, Brit. J. Ophth. 47: 290, 1963.

46. Miller, A., Bader, R. A. and Bader, M. E.: The neurologic syndrome due to marked hypercapnia, with papilledema, Amer. J. Med. 33: 309, 1962.

47. Stevens, P. M., Austen, K. F. and Knowles, J. H.: Prognostic significance of papilledema in course of respiratory insufficiency, J. A. M. A. 183: 161, 1963.

48. Grass, H. H.: Papilledema and pseudomotor cerebri following poliomyelitis, Am. J. Dis. Child. 93: 640, 1957.

49. Capriles, L. F.: Intracranial hypertension and iron-deficiency anemia, Arch. Neurol. 9: 147, 1963.

50. Lubeck, M. J.: Papilledema caused by iron deficiency anemia, Tr. Am. Acad. Ophth. Otolar. 63: 306, 1959.

51. Dandy, W. E.: Intracranial pressure without brain tumor, Ann. Surg. 106: 492, 1937.

52. Moore, R. B.: Pseudotumor cerebri, Pediatrics 19: 266, 1957.

53. Greer, M.: Benign intracranial hypertension. V, Menstrual dysfunction, Neurology 14: 668, 1964.

54. Carton, C. A., Pascal, R. R. and Tennyson, V. M.: Hydrocephalus and vitamin A deficiency in the rabbit: General considerations, in Disorders of the Developing Nervous System, Springfield, Thomas, Fields and Desmond, Editors, 1961, p. 214.

55. Woodhall, B.: Anatomy of the cranial blood sinus with particular reference to the lateral, Laryngoscope 49: 966, 1939.