

Pseudotumor Cerebri

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SUMMARY: *Pseudotumor cerebri* is a clinical syndrome in which signs and, sometimes, symptoms of raised intracranial pressure are present but in which mental and neurological function are unaffected. Therefore, the diagnosis is reached after mass and other structural causes of raised pressure have been excluded.

Many causes of pseudotumour have been suggested, not all of them well documented. Pathogenesis, however, includes cerebral edema, increased cerebral blood volume, and decreased cerebro spinal fluid (CSF) absorption.

Except for the risk of vision in a minority of cases, the prognosis is excellent.

RÉSUMÉ: La "pseudotumor cerebri" est un syndrome clinique dans lequel des signes, et parfois même des symptômes, d'hypertension intracrânienne sont présents, mais également dans lequel les fonctions mentales et neurologiques sont intactes. Le diagnostic est donc confirmé seulement après l'exclusion de masses intracrâniennes ou des autres causes structurales d'hypertension.

Plusieurs causes de pseudotumor ont été suggérées, mais peu ont été documentées. La pathogénèse, cependant, inclue l'oedème cérébral, une augmentation du volume sanguin cérébral et une diminution de l'absorption du LCR.

Sauf en ce qui concerne certains risques pour la vision chez une minorité des cas, le pronostic est en général excellent.

Pseudotumor cerebri has been recognized since the late nineteenth century, yet it remains the subject of much controversy especially as to pathogenesis. It has acquired many names over the years, but only "Benign Intracranial Hypertension" and "Pseudotumor" survive in common use.

CLINICAL FEATURES

The signs and symptoms, when present, are those of raised intracranial pressure in an otherwise completely healthy person. There are no localizing features and nothing to suggest an intracranial mass, hydrocephalus, or toxic or altered metabolic state (Mathew et al., 1975; Vollbracht and Gilroy, 1976; Johnston, 1973; Traviesa et al. 1976; Greer, 1962, 1967, 1968; Powell, 1972; VanderArk et al., 1971; Ziai, 1973; Johnston, 1974; Guidetti et al., 1968).

Benign intracranial hypertension (BIH) is seen predominantly in females, the sex ratio varying from 2:1 to 8:1. Its onset tends to be abrupt in younger patients, while in those of forty years or older its development may be insidious and its course protracted. The disease has a peak incidence in the third and fourth decades and is uncommon after fifty (Weisberg, 1975; Johnston and Paterson, 1974; Boddie, et al. 1974).

Headache is the most frequently reported symptom and is described as generalized, throbbing, episodic, most severe in the early morning, and aggravated by straining, coughing, or changes in position (Weisberg, 1975; Guidetti et al., 1968). Typically, it is relieved by mild analgesics. Visual disturbance is another major subjective complaint and may take the form of diplopia (usually on horizontal and distant gaze), blurred vision, transient obscurations and, rarely, visual field

constrictions (Weisberg, 1975; Powell, 1972; Grant, 1971; Boddie et al., 1974; Bradshaw, 1956; Paterson et al., 1961). Nausea is frequent but vomiting is uncommon. Tinnitus and dizziness with a rotational component may be reported.

Similarly, the signs are confined to those produced by persistently elevated intracranial pressure. Some authors state that bilateral (but not necessarily symmetrical) papilledema is the sine qua non of pseudotumor (Powell, 1972; Boddie, et al., 1974; Bradshaw, 1956; Paterson et al., 1961). There are, however, several reports of either no papilledema or of papilledema affecting only one eye. These have been explained on the basis of congenital or post-inflammatory obliteration of one or both optic subarachnoid spaces or by occlusion of the spaces by downward herniation of optic nerves and chiasm into the sella turcica in association with the empty sella syndrome (vide infra) (Weisberg et al., 1975; Kirkham et al., 1973; Lipton and Michelson, 1972; Foley and Posner, 1975). In infants, a full anterior fontanelle may be palpated. In all cases, the neck is supple (Weisberg, 1975).

Abducens nerve palsy, unilateral or bilateral, is a frequent finding. Decreased visual acuity and field defects are not uncommon; bilateral blind spot enlargement is almost universal. Unilateral or bilateral inferior nasal quadrantanopia may be demonstrated (Weisberg, 1975; Powell, 1972; Wilson and Gardner, 1966; Boddie et al., 1974; Guidetti et al., 1968).

One case is reported of a holocranial murmur synchronous with systole in a nineteen year old woman. This was thought to be due to carotid compression against the floor of the skull as a result of the intracranial

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hypertension (Lombaert and Carton, 1976).

INVESTIGATIONS

Pseudotumor cerebri is a diagnosis arrived at only after all other causes of intracranial hypertension and papilloedema have been excluded. Skull films are normal or, in protracted cases, may show the stigmata of raised intracranial pressure (ICP) (Capitanio and Kirkpatrick, 1969; Powell, 1972; Greer, 1967; Guidetti et al., 1968). An enlarged sella may be seen in cases associated with the empty sella syndrome and the radiographs of children may show suture diastasis (Weisberg, et al., 1975; Capitanio and Kirkpatrick, 1969; Foley and Posner, 1975; Greer, 1967). The EEG is often normal or may show diffuse slowing which clears with remission of the disease (Weisberg, 1975; Vollbracht and Gilroy, 1976; Powell, 1972; Greer, 1967; Guidetti et al., 1968). The opening pressure at lumbar puncture is elevated and the CSF protein is often slightly lower than normal. A mild elevation of CSF protein is compatible with BIH, but prolonged surveillance is needed in these cases to ensure than an intracranial mass or other cause of raised ICP has not escaped detection (Weisberg, 1975; Weisberg, 1975).

Carotid angiograms are normal or, in those cases where mastoiditis is associated with BIH, they may show lateral sinus thrombosis (Greer, 1967).

When angiograms are normal and show no evidence of either hydrocephalus or intracranial mass, air encephalography is safe and may be informative (Boddie et al., 1974; Greer, 1967). It will usually reveal ventricles of normal size; sometimes they are small. When, in longstanding cases, the ventricles are mildly dilated, the possibility of an obstructing lesion must be kept in mind during the prolonged follow up period (Mathew et al., 1975; Weisberg, 1975; Weisberg, 1975; Vollbracht and Gilroy, 1976; Powell, 1972; Boddie et al., 1974; Guidetti et al., 1968; Neville and Wilson, 1970).

The empty sella syndrome may be recognized on pneumoencephalography by air in the subarachnoid space which has herniated into the

sella turcica; the compressed hypophysis is seen as a filling defect inferoposteriorly (Weisberg et al., 1975; Weisberg, 1975; Foley and Posner, 1975).

Computerized tomography (CTT), where available, has made air encephalography unnecessary in the diagnosis of pseudotumor. It is more accurate and is without risk. The findings of normal or small ventricles, no displacements, and no masses in the scan are, in the appropriate clinical setting, characteristic of the condition (Delaney and Schellinger, 1976; Weisberg, 1977; Huckman et al., 1976; Boddie et al., 1974).

The "empty sella" is a radiological diagnosis made on pneumoencephalography. It is seen more often in women than in men and is often completely symptomless. It indicates a congenitally deficient diaphragma or one with a very large hiatus. The term "empty sella syndrome" should only be applied to an empty sella associated with functional impairment of optic nerve and chiasm. When benign intracranial hypertension (BIH) is present in a patient with empty sella syndrome, there is a higher incidence of visual disturbance than when either condition occurs alone. This is due to downward herniation of optic nerves, chiasm, and tracts into the sella which compresses and distorts them and occludes the optic subarachnoid space. Hypopituitarism does not accompany the syndrome, whether it occurs alone or in conjunction with BIH (Weisberg et al., 1975; Weisberg, 1975; Folley and Posner, 1975).

ETIOLOGY

Many causes of pseudotumor cerebri have been suggested, not all of them well documented. Many reports deal with small numbers of cases, often only one or two. These papers frequently imply that the co-existence of another condition is sufficient to attribute causal significance to it. The high incidence of spontaneous remission in BIH further weakens the claim that many of these associated conditions are important in its etiology.

In children, transverse or sigmoid sinus thrombosis secondary to suppurative otitis media and mastoiditis used to be identified much more

often than in adults (Greer, 1967, 1968; Ziai and Abassioum, 1973; Grant, 1971.) Since the superior sagittal sinus usually drains into the right transverse sinus, the right ear is more often the seat of infection. In adults, the cause usually cannot be demonstrated (Weisberg, 1975; Carlow and Glaser, 1974; Johnston and Paterson, 1974), but occasionally head trauma with or without skull fracture may induce sinus thrombosis which in turn results in BIH (Johnston, 1973; Greer, 1968; Johnston and Paterson, 1974; Beller, 1964). Internal jugular vein thrombosis complicating intravenous alimentation (Saxena et al., 1976) and superior caval obstructions from any cause have, rarely, been held responsible (Saxena et al., 1976; Greer, 1967; Bradshaw, 1956).

Whatever the endocrinological reason may be, an association is frequently seen between BIH and young, obese women, often with menstrual irregularities (Rothner and Brust, 1974; Traviesa et al., 1976; Greer, 1964, 1965; Bradshaw, 1956; Paterson et al., 1961). Traviesa et al., (1976), reported BIH in three sisters and other authors have observed a familial incidence (Buchheit et al., 1969; Howe et al., 1973). Other variations in hormonal milieu, physiological and pathological, attributed to the etiology of BIH include the menarche (Greer, 1964), pregnancy (Traviesa et al., 1976; Greer, 1963; Paterson et al., 1961), prolonged systemic or, in infants, topical steroid therapy (Weisberg, 1975; Gerber and Mullan, 1974; Roussounis, 1976; Greer, 1967), Addison's disease (Oldstone, 1966), hypoparathyroidism (Gerber and Mullan, 1974; Greer, 1968; BMJ, Editorial, 1970), and oral contraceptives (Greer, 1968).

Infants and children recovering from malnutrition and psychosocial deprivation may exhibit the radiological sign of separation of the cranial sutures (Capitanio and Kirkpatrick, 1969; Bray and Herbst, 1973). The sign indicates raised intracranial pressure, but in this case is due to increased growth of the brain and requires no special attention. Treatment of cystic fibrosis and surgical closure of patent ductus arteriosus have caused BIH

(DiLiberti and O'Brien, 1975; Capitanio and Kirkpatrick, 1969; Bray and Herbst, 1973).

The administration of vitamin A in both excessive and low doses has been incriminated, and hypovitaminosis A has occasionally been found in children with BIH (Edmunds et al., 1973; Lombaert and Carton, 1976; Gerber and Mullan, 1974; Hayes et al., 1971; Hawkins and Burlon, 1974; Feldman and Schlezinger, 1970; Bass and Fisch, 1961; BMJ, Editorial, 1970).

Antimicrobials appear to have been responsible in numerous cases. Tetracycline, nalidixic acid, and nitrofurantoin are the agents most frequently cited (Sharma and James, 1974; Cohen, 1973; Mushet, 1977; Gerber and Mullan, 1974; Giles and Soble, 1971; Olson and Riley, 1966; Ziai and Abassioum, 1973; Greer, 1967; Rao, 1974). One case of BIH in a man on gentamicin therapy has been reported (Boe and Conner, 1973).

Galactokinase deficiency (Litman et al., 1975), hypovitaminosis D in a child (Hochman and Meijlszenkier, 1977), histiocytosis X (Jackson and Griffith, 1975), Sydenham's chorea (Chun et al., 1961), systemic lupus (Carlow and Glaser, 1974; Bettman et al., 1968), Wiskott-Aldrich syndrome (Greer, 1968; Ziai and Abassioum, 1973), acute iron deficiency anaemia (Greer, 1967, 1968; Ziai and Abassioum, 1973; BMJ, Editorial, 1970) and psychotropic drugs (Weisberg, 1975; Gerber and Mullan, 1974) are among the remaining conditions claimed to be of etiological significance.

The association between high CSF protein in Guillain-Barré syndrome and in spinal tumors, with raised intracranial pressure, though rare, is well recognized (Weisberg, 1975; Greer, 1968; Janeway and Kelly, 1966). Presumably, in these cases, the raised CSF protein interferes with CSF absorption at the arachnoid villi. If that is so, the distinction between BIH and communicating "low pressure" hydrocephalus is a fine one.

PATHOGENESIS

The Role of Cerebral Edema:

Sahs and Joynt (1956) demonstrated edema by light microscopy in brain

biopsies on three patients with BIH. The small ventricles sometimes seen on ventriculography are assumed to be due to edema. Radiological evidence for edema, however, cannot by itself be taken as conclusive. Increase in brain volume may be due to an increase in blood volume necessary to maintain a constant blood flow in BIH (Johnston, 1973; Bayes et al., 1971; Boddie et al., 1974; Bradshaw, 1956).

The absence of neurological impairment, particularly of consciousness, is a serious objection to the theory that cerebral edema is the main cause of BIH (Johnston, 1973, 1974, 1975; Bradshaw, 1956). Another difficulty with that theory is the observation, made when subtemporal decompression was frequently performed for BIH, that the decompression was not "used", the area remaining soft and concave rather than tense and bulging (Wilson and Gardner, 1966).

High blood estrogen levels are known to cause hypoadrenal states, and increased brain water has been observed in estrogen fed rats. Therefore, it is possible that high estrogen states — pregnancy, menarche and oral contraceptives — can cause adrenal steroid suppression and cerebral edema. Correlation between the time of onset of BIH in gravid women and the estrogen rise in early gestation has been observed (Powell, 1972; Greer, 1964).

In obesity, an excessive fraction of circulating steroids is held in body fat. The resulting relative hypoadrenalism could cause cerebral edema leading to pseudotumor. Withdrawal of therapeutic steroids may have the same effect through adrenal suppression (Powell, 1972; Greer, 1965).

The Role of Cerebral Blood Volume (CBV):

A study in two patients revealed a marked elevation of CBV [disproportionate to the rise in cerebral blood flow (CBF)] in the acute stages of pseudotumor, which suggested dilatation of cerebral vessels. Reduction of intracranial pressure by lumbar puncture failed to reduce CBV. The conclusion was that the increased CBV was primary, and not a homeostatic response to intracranial hypertension. Here, too, endocrinopathies were cited

as possible causes of cerebral vasodilatation and the analogy was made to oral contraceptives which caused loss of vascular tone in leg veins (Mathew et al., 1975).

If, however, BIH is to be regarded as the result of a primary increase in CBV, this must be reconciled with the observation that secondary increases in CBF and CBV are invariable consequences of any rise in intracranial pressure, whatever the cause (Johnston, 1975). Nevertheless, in those cases of BIH due to obstructed venous return, this mechanism could be responsible (Johnston, 1974).

Impairment of CSF Absorption:

The rate of flow of CSF out of the subarachnoid space is governed by two factors: the pressure gradient between the subarachnoid space and the dural venous sinuses, and the resistance to flow across arachnoid granulations. Thus, any hormonal or vitamin imbalance which alters the permeability of the arachnoid villi to CSF will produce an increase in ICP as CSF volume rises; these hormonal or vitamin effects have been demonstrated experimentally in animals (Lombaert and Carton, 1976; Johnston, 1973, 1974, 1975; Hayes et al., 1971; Bercaw and Greer, 1970.)

Dural venous sinus thrombosis decreases the pressure gradient between the subarachnoid space and cerebral venous outflow to give a similar effect and venous distension behind the site of thrombosis contributes to elevated ICP (Johnston and Paterson, 1974; Bercaw and Greer, 1970).

Other evidence points to the role of decreased CSF absorption. Distended subarachnoid cisterns from which CSF gushes at craniotomy have been observed in patients with BIH (Johnston, 1975; Johnston and Paterson, 1974; Greer, 1962, 1963, 1967; Bradshaw, 1956). Low CSF protein levels are commonplace in pseudotumor patients as are high Ayala indices* suggesting high CSF volumes. Intracranial pressure monitoring in patients with BIH showed repeating cycles of pressure build-up, culminating in a rapid drop to near normal levels; this was thought to be

due to villous obstruction which yielded at a critical pressure level to allow sudden venting of CSF (Johnston and Paterson, 1974). Isotope cisternography studies in BIH have shown reduced CSF absorption; the possibility of increased CSF production in BIH was ruled out when CSF formation rates were found to be below normal. The patency of ventricular and subarachnoid spaces has been demonstrated in studies which show identical pressures in each compartment in patient with BIH (Johnston, 1973, 1975; Johnston and Paterson, 1974; Bercaw and Greer, 1970).

The absence of ventricular dilatation is consistent with the theory of impaired CSF absorption. The subarachnoid cisterns are the most capacious of the CSF spaces and preferentially accommodate excess CSF. Only when CSF volume becomes very high for a prolonged period will the ventricles dilate (Weisberg et al., 1975; Weisberg, 1975; Johnston, 1973, 1975; Powell, 1972; Johnston and Paterson, 1974; Guidetti et al., 1968).

$$*Ayala\ index: \frac{V \times P}{O}$$

where V is volume of CSF removed by LP.
 P is closing CSF pressure.
 O is opening CSF pressure.

DIAGNOSIS

BIH is the most benign of many causes of raised ICP without localizing signs. Therefore, the diagnosis is made by exclusion. Furthermore, the diagnosis is only secure when long-term follow-up has failed to reveal other disease processes; this is especially important in cases where atypical findings are noted (i.e. unilateral papilledema, slightly elevated CSF protein, dilated ventricles, etc.)

In addition to the non-specific signs and symptoms already mentioned, the absence of epilepsy and an unaffected mind are essential to the diagnosis (Weisberg, 1975; Greer, 1967; BMJ Editorial, 1970). EEG, skull films, echoencephalogram, and radioisotope brain scan should all be normal, although diffuse slow wave activity on EEG and radiological signs of increased ICP are acceptable. A

lumbar puncture should show only elevated opening pressure and normal or decreased CSF protein (Weisberg, 1975). When all these tests have been done, the CTT scan is preferable to angiography or air studies (Delaney and Schellinger, 1976; Weisberg, 1977; Huckman et al., 1976; Boddie, et al., 1974). Should the CTT scan (or pneumography and angiography) prove normal the diagnosis of pseudotumor is established. Long term follow-up is essential, since these investigations will miss 5% of brain tumors (Delaney and Schellinger, 1976). Misdiagnosis in one study occurred in 3.5% of cases, but this could have been improved upon by rigid adherence to these diagnostic criteria (Johnston and Paterson, 1974). A misdiagnosis rate of 25% has been reported in another paper, largely due to misinterpretation of CSF pressure data and mistaken identification of papilledema (Johnston and Paterson, 1974). The authors also advocated CSF pressure monitoring, fluorescein angiography, and isotope cisternography to support the diagnosis.

TREATMENT

Many forms of treatment, medical and surgical, have been tried with varying degrees of success. Many cases, perhaps the majority, recover spontaneously after one to three months, which makes assessment of treatment difficult (Powell, 1972; Grant, 1971; Boddie, et al., 1974; Greer, 1967; BMJ Editorial, 1970).

If the cause is known or suspected, withdrawal or correction of it will give relief in a high proportion of patients. Thus the treatment of suppurative otitis media should be undertaken if the sigmoid sinus is thrombosed in true "otitic hydrocephalus"; recently withdrawn steroids should be reinstated, and the withdrawal of an incriminated agent such as tetracycline or vitamin A will often be effective (Lombaert and Carton, 1976; Greer, 1968). Weight reduction in the obese may lead to a remission.

When a single lumbar puncture, performed for diagnostic reasons, apparently relieves the condition, a

spontaneous remission must be assumed to have occurred. More often, repeated punctures are required. Recurrence after lumbar puncture is stated by Weisberg (1975) to occur in 5% of patients, which is comparable to the recurrence rate for all cases of BIH.

Osmotic diuretics must be given intravenously, which imposes some limitations to their use. Their efficacy is in any case in doubt (Mathew, et al., 1975; Lombaert and Carton, 1976; Greer, 1967, 1968). Likewise, oral glycerol has been disappointing although some success has been reported (Mathew et al., 1975; Weisberg, 1975; Burde, et al., 1974). Acetazolamide, thought to decrease CSF secretion by inhibiting carbonic anhydrase, has not been impressive (Weisberg, 1975; Burde, et al., 1974; Greer, 1965, 1967).

Steroids have been used with some success. Steroids must be considered to have failed if no response is obtained in the first week. They should not be given for longer than two weeks; the recurrence rate in those cases that respond is very low (Weisberg, 1975; Carlow and Glaser, 1974; VanderArk et al., 1971; Paterson et al., 1961).

Surgical measures are employed when appropriate to the etiology (i.e. mastoidectomy for mastoiditis) or when vision, in the face of medical therapy, is in imminent danger.

Ventriculoperitoneal and lumboperitoneal shunting procedures have been effective. Because of the technical difficulty and increased risk of passing a ventricular cannula into a normal or small ventricle, a lumboperitoneal shunt is preferred; reports on lumboperitoneal shunting are generally favorable. The shunt may be removed following remission of the disease and rarely needs to be left in permanently (Weisberg, 1975; VanderArk, et al., 1971; Benini, 1973; Greer, 1967).

Subtemporal decompression is an effective although disfiguring procedure in cases resistant to more conservative measures. It has a 12% incidence of complications which include seizures, brain damage and CSF fistula. In some cases, serial lumbar punctures will still be required postoperatively (Weisberg, 1975; Vo-

lbracht and Gilroy, 1976; Greer, 1967, 1968; BMJ Editorial, 1970).

Bilateral optic nerve decompression is the surgeon's last resort in the prevention of visual deterioration. The procedure does nothing, of course, to relieve intracranial hypertension. Reports are favorable both as to its effectiveness and safety (Weisberg, 1975; Burde et. al., 1974; Galbraith and Sullivan, 1973).

PROGNOSIS

Pseudotumor on the whole carries an excellent prognosis, provided the correctness of the diagnosis is confirmed by long-term follow-up. Permanently impaired vision occurs only in a few patients, usually those who have had their disease for a long time (Powell, 1972; Johnston and Paterson, 1974; Guidetti et. al., 1968). Rarely, blindness may occur within a short time of onset of BIH (Howe et. al., 1973; Neville and Wilson, 1970); some authors, understandably, deplore the use of the term "benign" when such an outcome is possible.

The incidence of permanent visual impairment is 2% to 8% and includes decreased acuity and field defects, particularly inferior binasal quadrant-anopia (Weisberg, 1975; Wilson and Gardner, 1966; Johnston, and Paterson, 1974; Boddie et. al., 1964). The incidence of serious visual disturbance in children is reported to be lower than in adults (Grant, 1971). The combination of BIH and the empty sella syndrome probably has a higher incidence of permanent damage to vision (Foley and Posner, 1975).

The incidence of recurrence of BIH has been given as 0.2% to 12% by different authors. Most figures are nearer the upper end of this range. Recurrences almost invariably respond to treatment, while few remit spontaneously (Weisberg, 1975; Boddie et. al., 1974).

Once the condition has resolved without visual impairment, other complications will not arise later.

ACKNOWLEDGEMENT

The valuable advice and assistance of Dr. G. P. Morley, Professor of Neurosurgery, University of Toronto, in preparing this paper is gratefully acknowledged.

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