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Pseudotumour Cerebri
Incidence, Management and Prevention

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Contents

Abstract

Benign or idiopathic intracranial hypertension, also termed 'pseudotumour cerebri', is defined by the presence of raised intracranial pressure (ICP) in the absence of a focal intracerebral space-occupying lesion. The signs and symptoms of elevated intracranial pressure are also observed such as headaches, nausea and vomiting, elevated arterial pressure and, often, bradycardia. Somnolence and palsy of the abducens nerve are occasionally observed, while papilloedema causing reduction of visual acuity and blindness is a particularly defining feature.

Pseudotumour cerebri can be caused by a number of drugs, including tetracycline and quinolone antimicrobial agents; retinoids such as retinol (vitamin A), tretinoin and isotretinoin; and hormonal preparations including estrogens and their derivatives, growth hormone and thyroid hormone. Immunosuppressive agents, antineoplastic agents, lithium and drugs which interfere with neurotransmitter action have been less commonly reported to cause the condition.

Various illnesses can also be associated with pseudotumour cerebri including disseminated lupus erythematosus, sarcoidosis and Behcet's disease, haematological disorders, infectious diseases including borreliosis and AIDS, cystic fibrosis, chronic renal failure, obesity, and hormonal conditions pertaining to the thyroid and corticosteroid hormones.

Pseudotumour cerebri may be the result of a disorder of CSF dynamics (comprising either an obstruction of cerebral venous outflow, obstruction of CSF absorption in the arachnoid granulations, or CSF hypersecretion) causing interstitial brain oedema and consequent elevation of ICP. Indications of this are, in particular, increased water diffusion rates in the brain (as demonstrated by diffusion magnetic resonance imaging) and, possibly also, vascular congestion, although evidence for increased cerebral vascular volume is conflicting. In other instances, cytotoxic brain oedema may occur which both clinically and radiologically mimics true pseudotumour cerebri.

The treatment of cases without visual disturbances consists of bodyweight control if the patient is obese, and the administration of acetazolamide or diuretics [e.g. furosemide (frusemide)], and glucocorticoids when an inflammatory factor is involved. In patients with visual impairment, more urgent treatment is required; the treatment of choice is a lumbar CSF tap, lumbar CSF drainage, or a CSF diversion procedure, in some centres preceded by optic nerve sheath fenestration.

Prevention of pseudotumour cerebri should be directed at the avoidance of treating a patient who has a predisposing factor (such as obesity) with a drug known to cause pseudotumour cerebri, or of combining several drugs known to be associated with the condition such as a retinoid and a tetracycline.

1. Definition

Pseudotumour cerebri and benign or idiopathic intracranial hypertension are the terms currently used in the literature to describe the clinical condition first recognised by Dandy[1] in 1937. He described a clinical entity in an alert patient comprising the symptoms and signs of elevated intracranial pressure (ICP), particularly, papilloedema and elevated CSF pressure (exceeding 250mm water), in the absence of abnormalities of CSF composition or neurological and anatomical abnormalities, such as asymmetry of the ventricular system, denoting a focal lesion.

2. Symptomatology

Since the cranial vault cannot expand, an increase in intracranial mass will sooner or later result in an elevation of ICP. It is the elevation of ICP that causes the complaints that call attention to the condition. These complaints include headaches, nausea and vomiting, often bradycardia, and occasionally somnolence and palsy of the abducens nerve. However, a particularly defining feature is papilloedema causing reduction of visual acuity and eventually leading to blindness when neglected (see also review by Digre and Corbett[2]).

Pseudotumour cerebri is mostly a self-limited disease, and the increase of intracranial mass is global.

Table I. Overview of intracranial space-occupying lesions

Main symptoms
Elevation of intracranial pressure, with symptoms of headaches, nausea, vomiting, papilloedema, diplopia
Consequences and causes
Focal lesions
Localised swelling → shift and compression of ventricle
• brain tumour • brain abscess • brain haemorrhage } usually associated with vasogenic brain oedema contributing to the mass effect
• brain cyst
• vasogenic brain oedema: located in white matter. Due to tumour, abscess, haemorrhage, infarction, trauma
Global lesions
Generalised brain swelling → compression of cerebral ventricles
• cytotoxic brain oedema (unless in regional ischemia: focal)
• osmotic brain oedema
• pseudotumour cerebri *sensu strictiori* = vascular congestion + interstitial oedema
Hydrocephalus
Dilatation of cerebral ventricles

Therefore, shifts of brain mass resulting in tentorial or tonsillar herniation are less likely to occur than when elevated ICP is caused by a rapidly expanding focal lesion such as a brain tumour.

3. Relationship to Other Intracranial Space-Occupying Lesions

The usual space-occupying lesions are brain tumours, brain haemorrhage, brain oedema, brain abscess, brain cysts and hydrocephalus (table I).[3,4]

Tumours, haematomas, abscesses and cysts are focal lesions. Brain oedema of the vasogenic type (fig. 1) usually accompanies these focal lesions and arises from disruption of the blood-brain barrier (BBB), contributing to their mass effect.

Other types of oedemas exist [cytotoxic, osmotic and hydrostatic (table II; fig. 1)] which may have a global distribution. Hydrocephalus, often comprising moderate to considerable enlargement of the ventricular system, also tends to behave as a global mass lesion.

3.1 Mechanisms

The diversity of conditions that are associated with pseudotumour cerebri suggests that several possible mechanisms, constituting disorders of CSF dynamics, may be responsible:[5,6] (i) chronic obstruction of cerebral venous outflow; (ii) deficiency of CSF absorption in the arachnoid granulations; and (iii) overproduction of CSF.

3.1.1 Chronic Obstruction of Cerebral Venous Outflow

Chronic obstruction of cerebral venous outflow in individuals with pseudotumour cerebri has been demonstrated by the observed elevation of pressure in the cerebral venous sinuses,[7] e.g. in the presence of tumours compressing the sinus.[8] In other instances, thrombosis of the venous sinuses occurs as a complication of infection of the middle ear or the paranasal sinuses, as a consequence of the use of estrogen-containing contraceptives (see section 4.2.3), or in association with a thrombopathy such as protein S or C deficiency. In contrast to chronic obstruction, acute thrombosis of the venous sinuses is a fulminating and potentially lethal condition, causing cerebral ischaemia with concomitant vasogenic brain oedema.

3.1.2 Deficit of CSF Absorption

A deficiency of CSF absorption in the arachnoid granulations is indicated by an increase of the resistance to CSF outflow. The conditions that are associated with pseudotumour cerebri on the basis of this mechanism include infectious diseases and haematological and autoimmune conditions (see section 4.1.1), which presumably evoke infiltration of inflammatory cells in arachnoid granulations. Occasionally, pseudotumour cerebri has also been observed in conditions with elevated CSF protein levels, such as Guillain-Barré syndrome,[9,10] presumably as a result of the blockade of the absorption pathways in the arachnoid granulations. Withdrawal of cortisol in pretreated dogs reduced CSF absorption and increased CSF outflow resistance.[11] Vitamin A (retinol) deficiency, which is known to be associated with pseudotumour cerebri (see section 4.1.2), appears to induce fibrotic changes in arachnoid granulations and the meninges.[12]

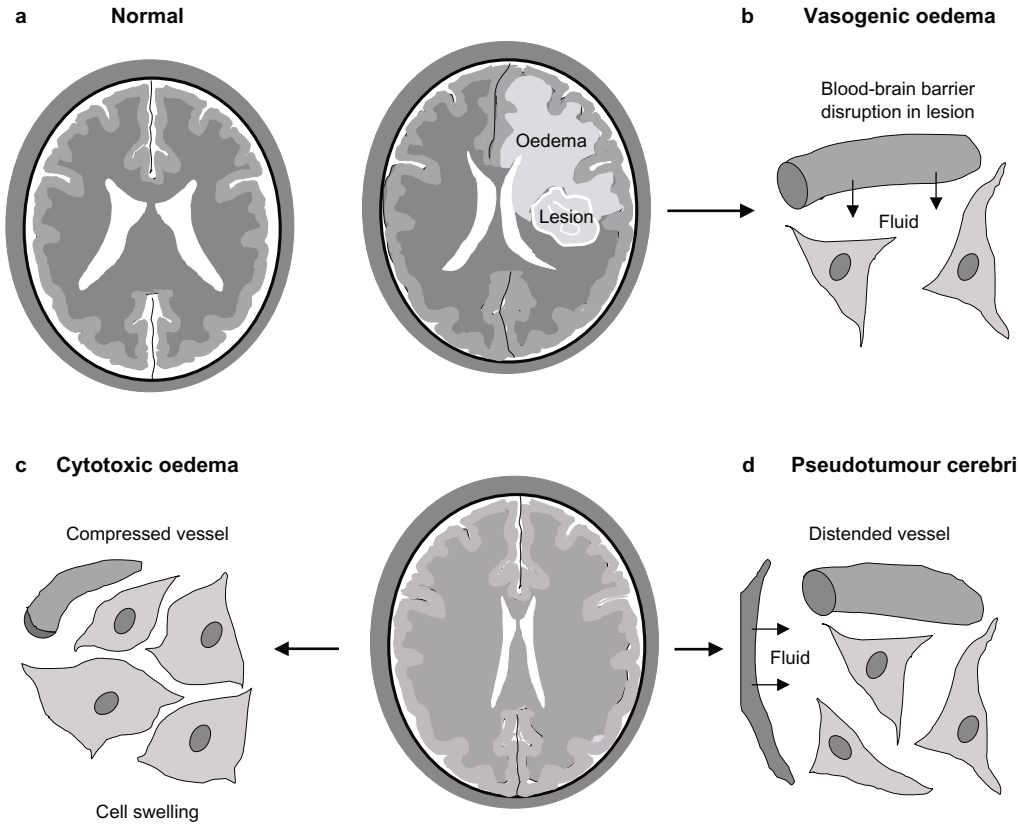

Fig. 1. Schematic drawing of brain magnetic resonance imaging scans depicting: (**a**) a healthy brain; (**b**) vasogenic oedema with a finger-like distribution pattern around a focal lesion (tumour, haemorrhage etc.), in which the blood-brain barrier is disrupted and plasma constituents leak out into the tissue; (**c**) generalised brain swelling due to cytotoxic oedema, in which cell swelling occurs possibly caused by global ischaemia, metabolic disorders or poisoning; and (**d**) pseudotumour cerebri with generalised brain swelling due to vascular congestion and interstitial oedema with fluid entering from the ventricle.

3.1.3 Overproduction of CSF

An overproduction of CSF, even that amounting to only 2 to 4 times the normal rate, has been demonstrated in obese young women with pseudotumour cerebri.[6] Hypersecretion of CSF has been suggested in hypervitaminosis A, by the observation of low CSF protein levels, which may cause excessive dilution.[13] Pseudotumour cerebri associated with the administration of growth hormone (GH; see section 4.2.3) is thought to result from stimulation of CSF secretion by insulin-like growth factor I (IGF-I), the production of which is stimulated by GH.

3.2 Differential Diagnosis

It should be noted that the mechanisms mentioned in section 3.1 are the same as those involved in the genesis of hydrocephalus. However, in hydrocephalus there is, in addition, obstruction of the CSF pathways, preventing free movement of CSF between the ventricles and the subarachnoid spaces. This results in the generation of a pressure head across the brain mantle which is directed outward from the ventricles to the subarachnoid spaces, and acts as the driving force for ventricular enlargement.[14] In contrast, in pseudotumour cerebri there is free communication between the ventricles and

the subarachnoid spaces and no pressure head across the brain mantle causing ventricular dilatation. The ventricular system is often narrow, although the ventricles may resume their normal size or become slightly enlarged when the condition has existed for some time.[7,15]

There have been indications that pseudotumour cerebri is associated with increased cerebral blood volume,[16,17] although this was refuted in a later study.[18] An increase of cerebral blood volume would be compatible with vascular congestion as a result of the chronic or subacute obstruction of cerebral venous outflow.

Another classical observation in pseudotumour cerebri was the histological evidence of interstitial oedema in the brain,[19] although histological observations of brain oedema tend to be invalidated by fluid shifts in the tissue inherent to the procedure of fixation.[20] Other evidence in support of the presence of interstitial (or hydrostatic) oedema in pseudotumour cerebri came from the measurement of the rate of water diffusion in tissue by means of diffusion magnetic resonance imaging (MRI). This parameter appeared to be increased in the periventricular regions or in the whole brain. Such oedema is presumably the result of transependymal water flow from the ventricle into the brain tissue.[21] This finding confirmed an earlier conventional MRI study which revealed an increased signal intensity in the periventricular white matter suggesting a low level of oedema.[22]

In other reported cases of benign intracranial hypertension without evidence of disorders of CSF dynamics, the increase of brain mass may actually have comprised a form of cytotoxic brain oedema (table II; fig. 1). This is a type of brain oedema in which fluid accumulates within the cells, in contrast to vasogenic brain oedema which results from the leakage of plasma constituents into the tissue through a disrupted BBB. The rate of water diffusion in the tissue, as shown by diffusion MRI, is characteristically decreased in cytotoxic oedema,[23] which may be accounted for by a reduction in extracellular space as water shifts into the cells (whereas in the interstitial oedema associated with pseudotumour cerebri water diffusion is increased, indicating an enlarged extracellular space). Common examples of cytotoxic brain oedema are: (i) the oedema associated with the early stage of ischaemia or other conditions associated with deficient cellular energy metabolism; and (ii) the oedema caused by poisoning with antimetabolites.

Hydrostatic or interstitial oedema (fig. 1; table II) arises as a result of a hydrostatic gradient, usually caused by elevated ventricular pressure (in hydrocephalus or pseudotumour cerebri) in conjunction with vascular congestion (in pseudotumour cerebri).

Osmotic brain oedema is a rare and short-lasting type of brain oedema, which is due to the influx of water from the blood into the brain. This occurs in conditions in which the blood plasma is hyposmolar with respect to brain, such as in water intoxication or hyposmolar hyperhydration.

As a rule, vasogenic brain oedema is localised in its distribution, occurring around focal lesions with a disrupted BBB. This can be visualised by contrast enhancement on computed tomography

Table II. Classification of brain oedema

Type	Causes	Mechanism	Location	Fluid composition	Other features
Vasogenic	Focal lesions	Blood-brain barrier breakdown	Extracellular	Water, NaCl, plasma proteins	In white matter
Cytotoxic	Ischaemia, intoxications	Disturbance of cell metabolism	Intracellular	Water, NaCl	In grey and white matter, decreased water diffusion
Osmotic	Hyposmolar hyperhydration	Osmotic gradient	Intra- and extracellular	Water, (NaCl)	Increased CSF production rate
Hydrostatic	Hydrocephalus pseudotumour	Hydrostatic gradient	Extracellular	Water, NaCl	Increased water diffusion

(CT) or MRI scans, and by the preferential accumulation in cerebral white matter with its pattern of finger-like protrusions. Therefore, as its definition rules out focal lesions, pseudotumour cerebri is not easily confused with vasogenic brain oedema.

On the other hand, cytotoxic oedema and osmotic brain oedema effect both white and grey matter, and they may present on scans only as a generalised swelling of the brain which is undistinguishable from pseudotumour cerebri *sensu strictiori* (i.e. true pseudotumour cerebri caused by the mechanisms mentioned in sections 3.1.1, 3.1.2 and 3.1.3). As in the majority of observations of pseudotumour cerebri the true nature of the condition is not resolved, it is conceivable that in a particular case cytotoxic or osmotic brain oedema may be involved. To resolve the true nature of benign intracranial hypertension associated with a particular condition or drug, diffusion MRI should be performed.

4. Incidence

In section 4.1, the conditions which have been reported to be associated with pseudotumour cerebri will be reviewed, while in section 4.2, drug-induced pseudotumour cerebri will be discussed. It is important to consider the interaction between these two causes. For example, certain pre-existing conditions such as obesity and chronic renal failure which *per se* may induce pseudotumour cerebri, may also contribute to the appearance of the condition during the administration of, for example, GH.[24] On the other hand, the influence of a pre-existing disease must always be considered when a drug is being investigated as the possible cause of pseudotumour cerebri.[25]

4.1 Unrelated to Drug Use

4.1.1 Haematological, Infectious and Inflammatory Diseases

Some disorders known to cause pseudotumour cerebri appear to be associated with thrombosis of the cerebral venous sinuses and, especially, infiltration of the arachnoid granulations by inflammatory cells. Conditions in which this has been demonstrated or suspected include systemic lupus erythematosus, neurosarcoidosis, Behcet's disease, certain infectious diseases (including Lyme borreliosis, psittacosis and infection with Yersinia pseudotuberculosis and HIV), Castleman's disease, and the syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions (POEMS).

Autoimmune and Haematological Disorders

Pseudotumour cerebri has often been observed in patients with systemic lupus erythematosus.[26-28] In this condition, a notable hypercoagulability of the blood and a high anticardiolipin antibody titre have been demonstrated in 58% of the patients, suggesting the involvement of thromboembolic events such as sinus thrombosis.[29-31] In other instances of lupus erythematosus, cerebral sinus thrombosis could not be demonstrated by cerebral angiography, but cisternography revealed delayed absorption of CSF. This implies that CSF absorption by the arachnoid villi could be disturbed in association with autoimmune mechanisms.[32]

Sagittal sinus thrombosis has also been shown to be responsible for pseudotumour cerebri in individuals with neurosarcoidosis,[33,34] and in some cases of Behcet's disease.[35-37] However, in these patients, a concomitant lymphocytic meningitis might also have affected CSF absorption with the possibility of encroachment of arachnoid granulations by inflammatory cells.

In one case of protein C deficiency, pseudotumour cerebri was attributed to sagittal sinus thrombosis.[38,39] In chronic myeloid leukaemia, impaired CSF absorption into the dural sinuses in relation to blood hyperviscosity was held responsible for pseudotumour cerebri,[40] although in these cases obstructive infiltration of the arachnoid granulations may also have been a likely cause.

Pseudotumour cerebri has been reported to occur in individuals with iron-deficiency anaemia.[41,42] A review of such cases has been presented by Tugal et al.[43] A case of idiopathic autoimmune haemolytic anaemia with pseudotumour cerebri[44] and of pseudotumour cerebri with essential thrombocythemia[45] in a patient with sickle-cell anaemia

possibly precipitated by pregnancy[46] have been reported.

In rare instances, pseudotumour cerebri has been reported in conjunction with Castleman's disease and angiofollicular lymph node hyperplasia[47] and the POEMS syndrome.[48-50] In the latter cases, papilloedema may occur in 33 to 84% of patients.[51]

Infectious Diseases

Lyme borreliosis has been cited in some instances as a cause of pseudotumour cerebri.[52-55] The condition has also been observed in patients with Yersinia pseudotuberculosis infection,[56] psittacosis[57] and HIV infection.[58,59] The mechanism by which pseudotumour cerebri is induced in infectious diseases may be the obstruction of CSF reabsorption in the arachnoid granulations by infiltrating inflammatory cells.

4.1.2 Vitamin Deficiency

Vitamin A deficiency in rabbits has been reported to be associated with pseudotumour cerebri.[60] In sheep with vitamin A deficiency, the mechanism responsible has been identified as fibrosis of arachnoid granulations and meninges.[12] Pseudotumour cerebri was also found in a patient with hypovitaminosis A combined with hyperthyroidism.[61] The significance of vitamin A in terms of causing pseudotumour cerebri was demonstrated by the marked decline in retinol-binding protein, which normally forms a stable protein-to-protein complex with transthyretin,[62] in rats with a deficiency of vitamin A. Transthyretin acts as a transporter of vitamin A and thyroid hormone. In contrast, pseudotumour cerebri may also be induced by hypervitaminosis A. The low protein level in the CSF of such patients suggests CSF hypersecretion.[13]

Vitamin D deficiency may also be associated with pseudotumour cerebri, as the condition has been identified in children with nutritional rickets.[63]

4.1.3 Hormonal Factors

In women with pseudotumour cerebri, an elevated CSF prolactin level has been observed,[64] with estrogen levels below the limit of detection. An elevated vasopressin level has also been found;[65] notably, vasopressin is known to be involved in brain water regulation.[66]

The glucocorticosteroid dexamethasone has been reported to decrease water permeability across the BBB, whereas its withdrawal or the administration of ethinylestradiol results in increased water permeability of the BBB and a consequent increase of cerebral cortical water content.[67] The role of corticosteroids in the development of pseudotumour cerebri is illustrated by a case of pseudotumour cerebri in a boy with Addison's disease,[68,69] and in a case following removal of an adrenocorticotropic hormone–secreting pituitary adenoma.[70] In dogs treated with cortisol, its subsequent withdrawal caused a significant reduction of CSF absorption and consequent increase of resistance to CSF outflow.[11]

Cases of primary hypothyroidism with pituitary hyperplasia have been reported to be associated with pseudotumour cerebri.[71,72]

Pseudotumour cerebri has been known to occur in individuals undergoing changes of hormonal status, such as menarche[73] and menopause,[74] but its occurrence during pregnancy has attracted particular attention.[75-77] Katz et al.[78] evaluated the incidence of pseudotumour cerebri in pregnant women and reported it to be approximately 1 in 870 births. Usually there are other factors which contribute to the appearance of pseudotumour cerebri in pregnancy, such as obesity[79] and deficiency of proteins S and C.[46] Indeed, pseudotumour cerebri was reported in 3 sisters who were obese during pregnancy[80] and a recurrence of pseudotumour cerebri was observed in obese women who failed to normalise their bodyweight after pregnancy or who became pregnant again.[81] In a patient with ovarian hyperstimulation syndrome, which is a complication of ovulation induction by exogenous gonadotrophins, pregnancy was associated with pseudotumour cerebri.[82]

Pseudotumour cerebri has been observed in young females who are morbidly obese.[83-85] In such individuals the CSF production rate has been found to be 2 to 4 times the normal rate; it was suspected that estrone was produced by the conversion of

androstenedione by adiposites.[6] Whereas the incidence of pseudotumour cerebri was 0.9 per 100 000 persons in the general population in the states of Iowa and Louisiana in the US, in obese females aged 20 to 44 years, the incidence was 13 to 15 per 100 000 in those 10% overweight and 19 per 100 000 in those more than 20% overweight.[86] In males who were obese the condition was less frequent, but showed the same age distribution.[2]

4.1.4 Other Factors

Chronic renal failure has been reported to be associated with pseudotumour cerebri.[87]

Pseudotumour cerebri has also been reported in patients with cystic fibrosis,[88-90] although in one of the cases, excessive administration of retinol to correct malnutrition may have been responsible.[88] Of 2 children with mucopolysaccharidosis, one developed pseudotumour cerebri and the other a communicating hydrocephalus, which suggested a similar underlying CSF absorption impairment.[91]

4.2 Drug-Induced

Pseudotumour cerebri has been reported to follow the use of a number of drugs, notably antimicrobial agents, retinoids and hormones. Unfortunately, the majority of reported instances of drug-induced pseudotumour cerebri are case reports, which prevents an estimation of the real incidence; this has only been assessed for isotretinoin and levonorgestrel.

4.2.1 Antimicrobial Agents

Pseudotumour cerebri has been reported, most notably, during the treatment of acne vulgaris with tetracyclins, such as minocyclin,[92-103] especially when combined with retinol[104] or tretinoin.[105] Gardner et al.[106] collected 37 cases of pseudotumour cerebri associated with tetracycline usage, the symptoms and sign of which resolved within hours to days after cessation of the drugs. The mechanism of induction has been suggested to be based on inhibition of adenylate cyclase in the arachnoid granulations, with this membrane enzyme allegedly being involved in receptor-mediated influences on CSF absorption in the arachnoid granulations.

Quinolones, such as nalidixic acid, have been proven to be the cause pseudotumour cerebri.[107-109] An overdose of nalidixic acid in infants was associated with the condition.[110] Similarly, the use of ofloxacin and ciprofloxacin[111,112] has been associated with the appearance of pseudotumour cerebri. On the other hand, withdrawal of aminoquinoline, a quinolone with dopamine agonist action, was reported to induce pseudotumour cerebri.[113]

Other antimicrobial agents which have been reported to be associated with pseudotumour cerebri include cotrimoxazole (trimethoprim-sulfamethoxazole),[114] nitrofurantoin[115] and amphotericin B.[116]

4.2.2 Retinoids

Retinol, a drug used for the treatment of acne vulgaris or psoriasis, is known to have the potential to induce pseudotumour cerebri.[117-120] The condition has been reported after the consumption of milk enriched with retinol and colecalciferol (vitamin D).[121] Pseudotumour cerebri has been implicated in the development of a bulging fontanelle in infants after retinol supplementation as part of an immunisation programme in Bangladesh.[122] Retinol toxicity as a cause of pseudotumour cerebri was suspected in 'liver lover's headache',[123] and in an individual consuming a strict diet of almost solely walnuts, ginseng tea and retinol supplements, although the patient was also severely iron-deficient and had cerebral sinus thrombosis.[124] On the other hand, a case of pseudotumour cerebri has been described as occurring in an individual with a combination of hypovitaminosis A and hyperthyroidism.[61]

Disorders of vitamin A metabolism have been considered to affect CSF secretion by an effect on the choroid plexus, as this tissue is known to secrete transthyretin.[125] The role of retinol in the development of pseudotumour cerebri is also illustrated by the stable binding of retinol-binding protein to transthyretin.[62] In hypervitaminosis A, pathological cytochemical changes have been observed in the choroid plexus.[126] Furthermore, patients with pseudotumour cerebri and hypervitaminosis A exhibited low CSF protein levels, suggesting CSF hypersecretion.[13]

Another retinoid that can precipitate pseudotumour cerebri is tretinoin (all-trans retinoic acid), which is used for the treatment of acute promyelocytic leukaemia.[127-132] In a phase I evaluation of the drug in paediatric patients, pseudotumour cerebri developed in 3 of 8 patients given a dosage of 80 mg/m^2/day.[133] In another phase I trial, pseudotumour cerebri was found in 2 of 5 patients receiving 120 mg/m^2/day and in 1 of 6 receiving 90 mg/m^2/day.[134]

The use of tretinoin for the treatment of acne vulgaris has also been reported to cause pseudotumour cerebri.[135-138] Pseudotumour cerebri has also been reported during treatment of acne vulgaris with isotretinoin,[139] especially in combination with tetracycline.[140] The Adverse Drug Reaction Reporting System in the US received reports of 104 suspected adverse reactions in 93 patients taking isotretinoin, of which 15 concerned severe headaches, 4 of which could be attributed to pseudotumour cerebri.[141]

4.2.3 Hormonal Preparations

Estrogens, used as oral contraceptives, are known to induce venous thrombosis, including that affecting the cerebral sinuses. Pseudotumour cerebri has been seen in women receiving these agents, especially in those individuals with thrombopathies such as deficiency of proteins C and S. Pseudotumour cerebri has been reported as an adverse effect of levonorgestrel implantation.[142,143] Wysowski and Green[144] reported on the incidence of pseudotumour cerebri in the US as assessed by the Food and Drug Administration's (FDA's) MedWatch Spontaneous Reporting System. An incidence of 5.5 per 100 000 among users of levonorgestrel was identified, as compared with an incidence of 0.9 per 100 000 in the general population.[86]

Treatment with and withdrawal of danazol has been reported to be associated with pseudotumour cerebri.[145-149] This agent is used for the treatment of endometriosis and is a synthetic ethisterone derivative which is known to inhibit the release of luteinising and follicle-stimulating hormones. Regarding its possible mechanism of action in the induction of pseudotumour cerebri, it may be relevant that some cases of the condition occur in patients with carpal tunnel syndrome,[150] another sequel of danazol therapy.[151,152] Danazol-induced carpal tunnel syndrome is thought to be due to fluid retention in the carpal tunnel. One of the two patients with danazol-induced pseudotumour cerebri described by Hamed et al.[146] had cerebral venous sinus thrombosis whereas the other showed no apparent underlying cause.

Pseudotumour cerebri has been reported during the administration of recombinant human growth hormone (rhGH), usually in children with a GH deficiency.[153-156] In a study involving more than 19 000 children who were receiving rhGH treatment, Blethen et al.[87] reported that pseudotumour cerebri was more likely to develop in those children who received treatment for renal disease. In an FDA review on GH-induced pseudotumour cerebri,[87] a causal relationship between pseudotumour cerebri and rhGH treatment was suggested by the appearance of symptoms soon after starting treatment and the disappearance of symptoms after cessation of treatment. It has been suggested that GH stimulates the production of IGF-I, which in turn stimulates the secretion of CSF by the choroid plexus, a structure which possesses a high level of IGF-I receptors.[157] Moreover, GH may cause sodium retention via the acute stimulation of the renin-angiotensin system.[158] Indeed, recombinant IGF-I, which has been used to treat patients insensitive to GH, has also been proven to cause pseudotumour cerebri.[24,159]

Pseudotumour cerebri has been reported during the use of leuprorelin, a synthetic nona-peptide analogue of leutenising hormone-releasing hormone (LH-RH).[160,161] The treatment of undescended testicles with beta–human chorionic gonadotrophin was reported to be followed by pseudotumour cerebri.[162]

Curiously, octreotide, a long-acting somatostatin analogue, was reported to reduce headaches and improve visual acuity in 3 patients with pseudotumour cerebri.[163]

Another hormone which can be associated with pseudotumour cerebri is thyroid hormone. For example, the condition has been associated with the

use of L-thyroxine replacement therapy in individuals with hypothyroidism.[164-171] However, it should be noted that hypothyroidism *per se* may be a cause of pseudotumour cerebri (see section 4.1.3).[72] Similar to vitamin A, which is also transported by transthyretin, disturbances of thyroxine level may induce the choroid plexus to secrete transthyretin and CSF.

The antiarrhythmic agent amiodarone, a drug which is a structural analogue of thyroid hormone, has been known to induce pseudotumour cerebri.[172-177] It may well be that its actions, including the induction of pseudotumour cerebri, are attributable to interaction with thyroid hormone receptors. In this respect it should be noted that the half-life of its action is in the range of weeks to months after withdrawal.

A case of pseudotumour cerebri was reported in a patient who had an excessive fluid intake and who was receiving intranasal oxytocin.[178] However, as there was concomitant hyponatraemia, the condition might actually have been a case of osmotic brain oedema.

Withdrawal of corticosteroids has been known to cause pseudotumour cerebri; 2 patients who had inflammatory bowel disease,[179] one patient with asthma[180] and another taking the drugs as replacement therapy for Cushing's syndrome[181] developed the condition after withdrawal of these agents.

4.2.4 Immunosuppressive Agents

Pseudotumour cerebri was reported during the use of cyclosporin for the management of tissue rejection after allogenic bone marrow transplantation.[182] Immunosuppressive treatment comprising cyclosporin, azathioprine and prednisone was held responsible for pseudotumour cerebri with visual loss progressing to blindness in a girl who had undergone an orthotopic heart transplant.[183]

4.2.5 Antineoplastic Agents

Chemotherapeutic agents such as cytosine arabinoside,[184] busulfan/cyclophosphamide (cytoxan),[185] and cisplatin, vinblastine and bleomycin.[186] have been reported to be associated with the development of pseudotumour cerebri.

4.2.6 Drugs Interfering with Neurotransmitter Action

Pseudotumour cerebri was associated with the withdrawal of the non-ergot dopamine agonist aminoquinoline.[113] A case of pseudotumour cerebri has been described in a child treated with mianserin, an antidepressant which inhibits the reuptake of noradrenaline (norepinephrine) by synaptic vesicles.[187]

Pseudotumour cerebri has been reported in a case of chronic poisoning with lindane (benzene hexachloride),[188,189] an agent which belongs to the insecticide group of chlorinated hydrocarbons known to enhance the release of neurotransmitters from presynaptic axon terminals. The mode of action of lindane in the development of pseudotumour cerebri may involve an effect on neurotransmitter-operated ion channels. In other conditions such as cerebral ischaemia, stimulation of these channels causes increased influx of ions with osmotically obliged water and consequent cell swelling (cytotoxic oedema).

4.2.7 Miscellaneous

Pseudotumour cerebri has been described in patients treated with lithium.[190-195] Multiple factors have been considered as the responsible mechanisms for lithium-induced pseudotumour cerebri in light of the properties of this drug, such as replacement of intracellular sodium, interference with the Na/K-ATPase pump (which may induce cell swelling, i.e. cytotoxic oedema), or interference with the Na/K-ATPase pump of the arachnoid villi (which is involved in CSF absorption).[196]

Intracranial hypertension has been reported in 2 patients treated with aspirin (acetylsalicylic acid), which promptly regressed after discontinuation of the drug.[197] In these cases, cytotoxic brain oedema rather than true pseudotumour cerebri may have been responsible for the ICP elevation. There are no other reports in the literature of an association between pseudotumour cerebri and the use of other nonsteroidal anti-inflammatory drugs.

5. Management

5.1 Unrelated to Drug Use

The treatment of pseudotumour cerebri which is not drug-induced involves the use of conservative measures initially. In obese patients, bodyweight control by dietary measures has been shown to reduce papilloedema,[198] and a recurrence of the syndrome was reported when normalisation of bodyweight was not achieved.[79] When pseudotumour cerebri has occurred during a previous pregnancy, this should not be taken as an contraindication for future pregnancies, although close monitoring is warranted.[81]

In milder cases without visual loss, acetazolamide,[198-200] which is known to inhibit CSF production, is recommended at a dosage of 250mg 3 times daily for adults and 8 to 30 mg/kg bodyweight for children. The disadvantages of this drug are: (i) the risk of developing metabolic acidosis, especially in the elderly and patients with diabetes mellitus; and (ii) the appearance of symptoms such as paraesthesias, somnolence, mental depression and confusion when the dosage is too high, although these symptoms soon disappear when the dosage is reduced.

A diuretic[200] such as furosemide (frusemide) can also be used, at a daily dose of 60 to 120mg for adults and 1 to 3 mg/kg bodyweight for children. As it acts by the withdrawal of systemic water resources, there is the risk of systemic dehydration with orthostatic hypotension, as well as the development of hypokalaemia and disturbances of renal function, with the use of the drug.

Glucocorticosteroids have been employed, with beneficial effect.[201,202] Their use is especially relevant in cases such as Behcet's disease in which inflammatory cells may block CSF absorption in the arachnoid granulations. However, prolonged use should be regarded with caution, as rebound of pseudotumour cerebri may occur after cessation.[179-181]

In more severe cases, and certainly in those individuals who have a reduction of visual acuity and imminent blindness, repeated lumbar punctures[203] or lumbar CSF drainage through a catheter inserted by lumbar puncture are recommended. These procedures are intended to be temporary measures in patients who are not expected to have a prolonged course, as they carry a risk of infection.

Surgical procedures may eventually be required in those patients with imminent loss of vision. In the past, this would have involved subtemporal decompression, which comprises the removal of temporal bone to allow outward expansion of the brain and lowering of ICP by enlarging the intracranial space. However, this procedure has the disadvantages of unaesthetic bulging and mechanical vulnerability of the uncovered area. Moreover, its effectiveness is limited as the protruding brain tends to plug the trepanation if the latter is made too small.

Currently, CSF diversion procedures (such as lumbo-peritoneal or ventriculo-peritoneal shunting) are the treatments of choice.[204] These are relatively simple interventions which achieve immediate amelioration of the symptoms as they address the disorders of CSF dynamics underlying the ICP elevation. The disadvantages of shunting are: (i) symptoms of intracranial hypotension, such as headaches and dizziness upon assuming the upright position, if a low-pressure valve is used [a medium-pressure valve usually suffices]; (ii) the risk of subdural haematoma when ICP is reduced too drastically by a low-pressure valve, although this complication is easily treated neurosurgically; (iii) in children a dysfunction of the shunting system tends to occur as the peritoneal catheter is withdrawn from the abdominal cavity during growth of the child; and (iv) the shunting system constitutes a foreign body which is liable to infection, and this may occur during the operation or during episodes of septicaemia following tonsillitis or cystitis.

In some medical centres, CSF diversion procedures are only performed when other options (namely, optic nerve sheath decompression[205,206]) have been tried and proven ineffective. Optic nerve decompression is intended to allow the CSF to escape through fenestrations made in the sheath of the optic nerve and thus prevent compression of the nerve. However, sectioning of Zinn's annulus, the narrowest point that the optic nerve passes through, is

usually refrained from. Optic nerve decompression has been reported to improve reduced vision, even bilaterally following a unilateral intervention. In other centres the procedure is regarded with some reservation, as it does not treat the underlying elevation of ICP with its symptoms of headache and vomiting. Furthermore, the improvement of vision may not always proceed satisfactorily and deterioration of vision may recur. Therefore, it is of paramount importance that the evolution of papilloedema, visual acuity, visual fields and visual evoked potentials are regularly checked by an ophthalmologist and a neurologist.

5.2 Drug-Induced

In cases of drug-induced pseudotumour cerebri, withdrawal of the drug usually proves sufficient to achieve an improvement in symptoms. Such an improvement has been suggested to provide evidence that a certain drug has caused the condition, particularly when there are dose/effect relationships and when the condition recurs upon resuming treatment.[87,106,197]

It is conceivable that in some cases, such as hormone replacement therapies, the drug in question cannot be discontinued as an adequate substitute is not available. This would require continuation of the drug regimen despite the presence of pseudotumour cerebri. In these cases, there should be concomitant control of ICP, primarily by conservative measures such as bodyweight control and acetazolamide, and in the presence of visual impairment by more drastic measures such as optic nerve sheath fenestration or CSF diversion procedures.

6. Prevention

The administration of a drug with the potential for causing pseudotumour cerebri in a patient with a condition known to be associated with pseudotumour cerebri, such as obesity or chronic renal failure, should ideally be avoided. However, it may not be warranted to abandon the use of the drug, since the incidence of pseudotumour cerebri is generally low and the symptoms tend to subside soon after discontinuation of treatment. The real danger resides in the unexpected and unrecognised appearance of intracranial hypertension. Therefore, any patient using a drug with the potential for evoking pseudotumour cerebri should be monitored carefully for the appearance of headaches, vomiting, diplopia and visual complaints. One should also be wary about using estrogen contraceptives in women with thrombopathies such as protein C or protein S deficiency. Furthermore, it is advisable to avoid a combination of drugs which each has the potential to induce pseudotumour cerebri, such as retinol and tetracyclines for the treatment of acne vulgaris, or tetracyclines with quinolones for the treatment of infections.

7. Conclusions

Although quite infrequent, the occurrence of pseudotumour cerebri should be considered as a possible adverse effect of drugs. When using drugs which are known to induce pseudotumour cerebri, patients should be notified and instructed to be alert for symptoms and signs of ICP elevation, notably a reduction of visual acuity. The same cautions apply to patients with diseases such as lupus erythematosus or Behçet's disease which have the potential of causing pseudotumour cerebri.

In patients in whom pseudotumour cerebri is suspected, CT and MRI scans are recommended, as is diffusion MRI in order to differentiate true pseudotumour cerebri from global types of brain oedema. Evidence of cerebral sinus thrombosis as well as blood clotting status should also be investigated.

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