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# Epidemiology and Risk Factors for Idiopathic Intracranial Hypertension

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### Keywords

idiopathic intracranial hypertension; pseudotumor cerebri; papilledema; epidemiology; risk factors

## Introduction

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by elevated intracranial pressure that usually occurs in obese women in the childbearing years. The signs and symptoms of intracranial hypertension are that the patient maintains an alert and oriented mental state, but has no localizing neurologic findings. There is no evidence of deformity or obstruction of the ventricular system and neurodiagnostic studies are otherwise normal except for increased cerebrospinal fluid pressure.[1] Neuroimaging signs of increased intracranial pressure include empty sella syndrome, smooth-walled venous stenoses, flattened globes and fully unfolded optic nerve sheaths. In addition, no secondary cause of intracranial hypertension can be found. This definition comprises the modified Dandy criteria for IIH.[2] There is considerable literature on IIH epidemiology, risk factors and secondary causes of intracranial hypertension. In this review, we will focus on cases of IIH where the modified Dandy criteria are met.

## Epidemiology

The annual incidence of IIH in the Western world is about 0.9/100,000 persons and 3.5/100,000 in females 15 to 44 years of age.[5, 6] However, the incidence can largely vary depending on location. For example, in Japan the incidence of IIH was found to be only 0.03/100,000,[3] whereas the incidence was reported to be 2.2/100,000 in Libya.[4] A summary of the epidemiological studies can be seen in table 1.[3–11] Differences in environmental factors, specifically obesity, likely play a role in the different incidences seen in these studies.

IIH is increasing in incidence in parallel with the current epidemic of obesity.[6] In a large population study involving Iowa and Louisiana, Durcan et al., found the incidence of IIH to be 19 per 100,000 among obese women aged 20 to 44 years who were 20% or more over ideal weight, compared to 0.9 per 100,000 in the general population.[6] Other population studies have confirmed that the vast majority of patients with IIH are obese women of childbearing age.[4,7,8,11] The mean age at the time of diagnosis is about 30 years.[12] The annual cost of IIH in the United States alone has been estimated to exceed 444 million

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dollars, mostly because of frequent hospitalizations and its predilection for young working-age adults resulting in a significant loss of productivity.[13]

Although less frequent, IIH can also occur in children, men, and the elderly.[14–16] In a retrospective study of IIH in the pediatric population, Cinciripini and colleagues found that IIH was rare in children, and interestingly found no gender predilection or higher rates of obesity in prepubescent children with IIH.[16] The lack of predilection for females and obesity in prepubescent children has also been seen in other large retrospective studies.[17–19] After puberty, obese females are more frequently affected, similar to adult onset IIH.

In adulthood, less than 10% of IIH patients are male. Like women, men affected with IIH are typically obese. However, studies suggest males may have worse visual outcomes than females with IIH.[15,20] In a retrospective review of 721 patients with IIH, men were twice as likely to develop severe vision loss compared to women.[15] Men were also more likely to have sleep apnea, report less headaches, and more likely to have visual changes as their first symptom of IIH.[15] The worse visual prognosis in men may be because they less frequently experience or report other symptoms of raised intracranial pressure, which may lead to more advanced disease on presentation.

There is no clear racial predilection for IIH. While the majority of epidemiological studies show fairly equal prevalence of IIH among different countries, there are a few studies that suggest IIH may be less prevalent among Asians.[3,21] This is mostly thought to reflect decreased obesity among some Asian countries. The incidence of obesity in the US is 33.5% among adult women compared to only 3% in Japan.[22,23] However, recent studies showed a lower prevalence of obesity among Asian patients diagnosed with IIH.[21,24] This suggests that obesity may not play as large a role in the development of IIH among Asians.

Although there is no difference in the prevalence of IIH between African Americans and Caucasians, African American patients with IIH may have worse visual outcomes compared to Caucasian Americans. In a retrospective review of 29 men, Digre and Corbett found that 3 of 4 African American males became blind from IIH.[20] Although this was a small number of patients, this observation was also seen in a larger retrospective review done by Bruce et al., who reviewed 197 black and 253 non-black patients with IIH and found that black patients were more likely to have severe vision loss in at least one eye.[25] These findings suggest ethnic differences and genetic background may influence the disease pathogenesis.

## Risk factors of idiopathic intracranial hypertension

Studies of conditions associated with IIH are mostly uncontrolled and retrospective. This has led to erroneous conclusions because investigators have tried to implicate IIH using chance and spurious associations with common medical conditions and medications. Also, there are a host of case reports of associations with IIH where the cases do not meet the modified Dandy criteria of IIH and therefore should be disregarded. Identifying true risk factors for IIH is important in making the diagnosis of IIH and also understanding the pathophysiology of the disease.

Table 2 lists the etiologies of intracranial hypertension that meet the modified Dandy criteria for IIH except that a cause is associated. The highly likely risk factors category is a list of cases with many reports of the association with multiple lines of evidence. Probable risk factors are reports with some convincing evidence. Possible risk factors have suggestive evidence or are common conditions or medications with intracranial hypertension as a possible rare association. Also listed are some frequently cited but poorly documented or unlikely risk factors; three case-control studies suggest the majority of these associations are not valid.[20,26,27] There is also a list of secondary causes of intracranial hypertension that can

mimic IIH, but have structural abnormalities or other reason for the raised intracranial pressure.

## Highly likely and probable risk factors

Given the relatively high prevalence of obesity in IIH patients, weight clearly plays a role in the disease process. A recent multicenter case control study demonstrated a correlation between body mass index (BMI) and the risk of IIH.[28] The study found a dose-response effect where increasing levels of BMI was associated with a progressively greater risk of IIH. In addition, the study found that relatively small amounts of weight gain, in the 5% to 15% range, was associated with an increased risk of developing IIH, even among non-obese patients.[28] In addition, other studies have demonstrated that increased weight is associated with recurrence of the disease.[29–31] A recent study by Ko et al. found a 6% weight gain among 26 patients with IIH recurrence, while 24 patients without recurrence had no change in weight.[30] In addition to contributing to the onset and recurrence of the IIH, studies also suggest that obesity may be a risk factor for visual loss among patients with IIH.[12,32] In a prospective study of 50 patients with IIH, Wall and George demonstrated that deterioration of visual fields was significantly associated with recent weight gain.[12] A recent retrospective review of 414 IIH patients also found an association between increasing BMI and the severity of papilledema and vision loss.[32] Although obesity is clearly associated with IIH, the mechanism of how it may cause IIH is unknown.

Gender is the other obvious risk factor because over 90% of patients affected with IIH are women. It is still not well understood why there is such a gender predilection for the disease. It is interesting that prepubescent children affected with IIH have no gender predilection, while onset of IIH within older children after puberty occurs predominantly in females.[16] This suggests that hormones are playing a role in the pathophysiology of the disease. In addition, sex hormones can be modulated by adipose tissue and obesity, which makes alterations in hormones a seemingly plausible disease mechanism. However, studies of hormonal differences in IIH have been inconclusive.[33–36]

Because female gender and obesity are the main risk factors for IIH, endocrine and hormonal changes likely play a role in the disease through an undetermined pathway. Other less common, but convincing endocrine abnormalities known to be associated with intracranial hypertension include Addison's disease,[37] hypoparathyroidism,[38] and growth hormone use in children.[39–41]

Another risk factor for intracranial hypertension is vitamin A intoxication. This phenomenon has been known for centuries by the Eskimo (Inuit) who hunt polar bears for fur and meat but avoid eating the liver for fear of the headaches and blurred vision that result from its ingestion. Polar bears have high hepatic vitamin A levels because they are at the top of the Arctic food chain, and therefore ingestion of the liver was likely inducing intracranial hypertension. Hypervitaminosis A associated with intracranial hypertension was further described by Gerber and colleagues in 1954 and is now a well-known association.[42,43] Other forms of vitamin A, such as isotretinoin (Accutane) for acne treatment and especially all-trans retinoic acid for the treatment of acute promyelocytic anemia have also been found to be associated with intracranial hypertension.[44–49] Given the clear association between vitamin A intoxication and intracranial hypertension, it has been hypothesized that the pathogenesis of IIH involves abnormal vitamin A metabolism. Interestingly, recent studies have found increased levels of unbound retinol in the cerebrospinal fluid (CSF) of patients with idiopathic intracranial hypertension that did not receive vitamin A supplementation.[50,51] It has been suggested that elevated levels of vitamin A may cause overstimulation of RAR α receptors in the central nervous system, resulting in increased intracranial pressure by impairing CSF absorption.[52,53] However, if altered vitamin A

metabolism is associated with IIH, there must be other factors influencing the disease because there is no evidence that vitamin A metabolism is different in women than men.

Case reports associating some other drugs appear convincing as well: tetracyclines and their derivatives,[54,55] nitrofurantoin,[56] indomethacin[57] or ketoprofen in Bartter's syndrome, [58] and thyroid replacement therapy in hypothyroid children.[59] While corticosteroid use is not associated with intracranial hypertension, steroid withdrawal clearly is linked (see Table 2).[60,61]

## Possible risk factors

The co-occurrence of obstructive sleep apnea and IIH has been well reported.[62–65] However, it is still debatable if this is because of the high prevalence of obesity in patients with IIH, which is clearly a risk factor of sleep apnea as well. A recent study suggested that sleep apnea is not an independent risk factor for IIH when other risk factors, such as obesity, are taken into account.[65] However, two prior studies have documented increased intracranial pressure during apneic periods in patients with IIH.[66,67] Jennum and Borgesen documented the occurrence of increased intracranial pressure during waking hours in the absence of apnea in half their subjects.[67] Since there is a biologically plausible mechanism to explain increased intracranial pressure in sleep apnea, we recommend sleep studies in all patients with symptoms suggestive of obstructive sleep apnea.

Other possible risk factors for intracranial hypertension include nalidixic acid,[68] lithium[69], systemic lupus erythematous,[70] hypophosphatasia,[71] among others (see Table 2).[72]

## Unlikely or unproven risk factors

Although steroid withdrawal and Addison's disease are clearly associated with intracranial hypertension,[60,61,73] as is hypoparathyroidism, links to other endocrine abnormalities remain unproven. For example, corticosteroid use has been associated with many suspected cases of intracranial hypertension; however, none of the cases fulfill the modified Dandy criteria.

Several other purported associations with IIH have been refuted by controlled studies. Pregnancy, irregular menses and oral contraceptive use have been shown to be simply chance associations.[6,27,74] In case-control studies, no association is found between IIH and multivitamin, oral contraceptive, corticosteroid or antibiotic use.[26,27]

Arterial hypertension has been found to be associated with IIH.[27,75] However, spuriously elevated blood pressure is commonly reported in obese people due to the use of standard size rather than oversize sphygmomanometer cuffs and obesity is associated with arterial hypertension. It is unlikely that there is a direct association of arterial hypertension and IIH.

## Secondary causes of intracranial hypertension

Many entities can cause raised intracranial pressure and mimic the signs and symptoms of IIH. Many have other symptoms or findings that make the diagnosis easier to distinguish, such as fever and mental status changes associated with meningitis. However, there are disease entities that will only present with signs and symptoms of raised intracranial pressure and therefore can only be diagnosed with neuroimaging or evaluation of the cerebral spinal fluid after lumbar puncture. Although these diseases can cause a clinical presentation identical to IIH, they are not idiopathic.

Large CNS lesions, especially if they grow very slowly, can sometimes cause raised intracranial pressure as their only presenting feature. Any disorder that causes decreased

flow through the arachnoid granulations or obstructs the venous pathway from the granulations to the right heart is accepted as a cause of intracranial hypertension because of its biologic plausibility. Dural venous sinus thrombosis is the classic masquerader for IIH. Arteriovenous malformations or dural fistulae with high flow may overload venous return and result in elevation of intracranial pressure. Other entities include superior vena cava syndrome, glomus tumors, and others (see Table 2).[72] Diseases that markedly increase the protein within the cerebral spinal fluid, such as Guillain-Barre syndrome or intraspinal tumors, can also lead to raised intracranial pressure.[76]

Because these diseases can masquerade as IIH and often require different treatment, it is important to obtain a MRI along with a lumbar puncture and often a MRV in patients with signs and symptoms of raised intracranial pressure

## Conclusion

Idiopathic intracranial hypertension is a disease of women in the childbearing years, and its prevalence is increasing due to the worldwide obesity epidemic. There are many risk factors that have been associated with IIH, many of which appear to be chance associations. Recognizing and understanding the risk factors that truly contribute to intracranial hypertension is important in both diagnosing and understanding the pathophysiology of the disease. There are also many diseases that cause intracranial hypertension that mimic IIH, which are important to recognize because the outcome and treatment are different depending on the etiology. Future results from the recently completed multicenter Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) will likely shed more light on the risk factors and pathogenesis of the disease.

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intracranial and intraspinal tumors, and in the Guillain-Barre syndrome. N Engl J Med. 1954; 250:932–6. [PubMed: 13165928]

**Table 1**

Summary of Epidemiological studies on IIH

| Study | Incidence (per 100,000/year) | Country |
|---|---|---|
| Radhakrishnan, et al., 1984 | 1.7 | Libya |
| Durcan et al., 1998 | 0.9 | USA |
| Radhakrishnan et al., 1993 | 0.9 | USA |
| Radhakrishnan et al., 1993 | 2.2 | Libya |
| Yabe et al., 2000 | 0.03 | Japan |
| Craig et al., 2001 | 0.51 | UK |
| Kesler et al., 2001 | 0.94 | Israel |
| Carta et al., 2004 | 0.28 | Italy |
| Raoof et al., 2011 | 1.57 | UK |

**Table 2**

Differential diagnosis of IIH (cases must meet the modified Dandy criteria of IIH except that a cause is found)

| |
|---|
| Highly likely risk factors |
| female gender |
| obesity/weight gain |
| endocrine disorders |
| Addison's disease |
| hypoparathyroidism |
| steroid withdrawal |
| growth hormone use in children |
| nutritional disorders |
| hypervitaminosis A (vitamin, liver or isotretinoin intake and all-trans retinoic acid for acute pro-myelocytic leukemia) |
| hyperalimentation in deprivation dwarfism |
| Probable risk factors |
| chlordecone (kepone) |
| ketoprofen or indomethacin in Bartter's syndrome |
| thyroid replacement therapy in hypothyroid children |
| tetracycline and its derivatives |
| uremia |
| Possible risk factors |
| sleep apnea |
| systemic lupus erythematous |
| amiodarone |
| hypovitaminosis A |
| iron deficiency anemia |
| lithium carbonate |
| nalidixic acid |
| sarcoidosis |
| sulfa antibiotics |
| hypophosphatasia |
| Unlikely or unproven risk factors |
| corticosteroid intake |
| hyperthyroidism |
| menarche |
| arterial hypertension |
| menstrual irregularities |
| multivitamin intake |
| oral contraceptive use |
| pregnancy |
| Secondary causes of intracranial hypertension |
| decreased flow through arachnoid granulations |
| scarring from previous inflammation (e.g. meningitis, sequel to subarachnoid hemorrhage) |

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| elevated protein (e.g. Guillain-Barre, intraspinal tumor) |
| obstruction to venous drainage |
| venous sinus thrombosis |
| hypercoagulable states |
| includes anabolic steroids and systemic lupus |
| erythematous |
| contiguous infection (e.g. middle ear or mastoid - otitic hydrocephalus) |
| bilateral radical neck dissections |
| superior vena cava syndrome |
| glomus tumor |
| increased right heart pressure |
| arteriovenous malformations and dural shunts |

The table lists the etiologies of intracranial hypertension that meet the modified Dandy criteria except a cause is associated. The *highly likely risk factors* category includes cases with many reports of the association with multiple lines of evidence. *Probable risk factors* have reports with some convincing evidence. *Possible risk factors* have suggestive evidence or are common conditions or medications with intracranial hypertension as a rare association. Also listed are some frequently cited but poorly documented or unlikely causes; three case-control studies suggest the majority of this group of associations is not valid. The *non-idiopathic intracranial hypertension* category is a list of diseases that can mimic IIH, but have a clear cause of raised intracranial pressure.