Neuro-ophthalmology Update

Idiopathic intracranial hypertension in the Middle East A growing (concern



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Abstract

Idiopathic Intracranial Hypertension (IIH) is a disorder of increased intracranial pressure without any identifiable etiology. It is defined by elevated intracranial pressure (ICP) with normal neuroimaging and normal cerebrospinal fluid (CSF) contents. IIH typically affects young obese women and produces symptoms and signs related to high ICP. Headache and blurred vision are the most common symptoms, and papilledema is the major clinical sign. In this review we examine the epidemiology and demographic features of IIH in Middle Eastern countries and compare and contrast them with the published IIH literature from Western countries. The incidence of IIH in several Middle East countries has been estimated at 2.02–2.2/100,000 in the general population, which is higher than the Western rate. Obesity is a major risk factor globally and it is associated with an increased risk of severe vision loss due to IIH. There has been an increase in obesity prevalence in the Middle East countries mainly affecting the Gulf Council Countries (GCC), which parallels increased industrial development. This rise may be contributing to the increasing incidence of IIH in these countries. Other risk factors may also be contributing to IIH in Middle East countries and the differences and similarities to Western IIH merit further study.

Keywords: Idiopathic intracranial hypertension (IIH), Pseudotumor cerebri (PTC), Epidemiology, Obesity, Middle East, Gulf Council Countries (GCC)

Production and hosting by Elsevier B.V. on behalf of Saudi Ophthalmological Society, King Saud University.

http://dx.doi.org/10.1016/j.sjopt.2014.09.013

Introduction

Idiopathic intracranial hypertension (IIH), also known as primary pseudotumor cerebri, is a disorder of increased intracranial pressure (ICP) with normal neuroimaging and CSF composition and no underlying etiology. IIH typically affects

obese women of childbearing age but it may be seen in patients of any age, in either gender, and without obesity. ²² Other risk factors for secondary IIH are the use of exogenous substances such as lithium, high doses of vitamin A, tetracyclines (especially minocycline), and corticosteroids (both with steroid intake or more likely following steroid withdrawal). ³⁵

Received 13 July 2014; received in revised form 10 September 2014; accepted 16 September 2014; available online 28 September 2014.

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The diagnosis of IIH is one of exclusion and the modified Dandy criteria are generally used to make the diagnosis (Table 1). 1,28 While once called "benign intracranial hypertension", the disorder is not necessarily a benign disorder as some may suffer significant vision loss related to papilledema and many may experience moderate to severe or intractable, disabling headaches. In this review, we consider the epidemiology and demographic features of IIH in the Middle East countries and compare and contrast with the published literature from Western countries.

Epidemiology and obesity

Incidence

Many epidemiological studies have documented the association of IIH with female gender and obesity. In the United States (US) the approximate annual incidence has been reported to be 0.9-1/100,000 in the general population. The incidence increases to 13-14.8/100,000 for women of ages 20-44 years who were 10% or more above ideal body weight (IBW) and the incidence increases to 19.3/100,000 for women in this age group when 20% or more above IBW. 16 The incidence varies from country to country probably related to the prevalence of the obesity in the respective region. In the Sheffield, UK study, the incidence was 1.56/100,000/year, 2.86/ 100,000 in women, and 11.9/100,000 in obese women. 18 The reported annual incidence of IIH in several Middle East countries has been estimated at 2.02-2.2/100,000 in the general population which is even higher than the Western statistics. A study conducted in Libya demonstrated an annual incidence of 2.2/100,000 in the general population, 4.3/100,000 in women, 12/100,000 in women aged 15-44 years and 21.4/ 100,000 in obese women. ¹⁷ Another study performed in Oman estimated an annual incidence of 2.18/100,000 in the general population, 3.25/100,000 women in all age groups, and 4.14/ 100,000 in the age group of 15-44 years. 14 The reported annual incidence of IIH in Israel was 2.02/100,000 in the general population, 3.17/100,000 in women and 5.49/100,000 in reproductive age group.²⁰

The increased incidence of IIH in these countries could be related to the globally increasing rates of obesity (Table 2).

Obesity prevalence

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. Body mass index (BMI), defined as a person's weight in kilograms divided by the square of height in meters (kg/m²), is a commonly used index to classify overweight and obesity in adults. The World Health Organization (WHO) defines overweight as a BMI of 25 or more and obesity as a BMI of 30 or more. ⁴⁰ In

its 2008 study of the global obesity epidemic, the WHO estimated that more than 1.4 billion adults who were overweight and more than half a billion were obese. The prevalence of obesity has nearly doubled between 1980 and 2008. Globally over 40 million preschool children were overweight in 2008.⁴⁰ The prevalence of obesity worldwide parallels the increased industrial development across the world, which in the GCC is related to the significant growth in incomes and the resulting rapid urbanization and improved living conditions. 41 Table 3 provides the 2010 WHO statistics for obesity in Western and Middle East countries. The rank order in Middle East countries for obesity in women is Kuwait 55.2%, Egypt 48%, and United Arab Emirates (UAE) 42%. These percentages are all higher rates than in any of the European countries and about the same as the US (48.3%) and Mexico (41%), Countries such as Bahrain (37.9%), Jordan (37.9%), Saudi Arabia (36.4%), Tunisia (32.6%), Qatar (31.6%), Iran (29.5%) and Lebanon (27.4%) also have higher obesity rates in females than in European countries and Israel (25.9%). The prevalence of overweight individuals is higher in men than women in Western and European countries, but in the Middle East countries, it is higher in women. Development, urbanization, and improved living conditions in the Middle East countries have led to greater consumption of higher calorie and potentially unhealthy food intake, decreased physical activity and more sedentary lifestyles, and an increase in the prevalence of obesity in people of all age groups, especially women.⁴¹

Role of obesity on IIH

A recent case control study showed that higher levels of weight gain and BMI were associated with a greater risk of IIH.³ Obese and non-obese patients with recent moderate weight gain (5–15% of their weight) also have a greater risk of IIH. Recent weight gain in newly diagnosed IIH is also common finding that has been reported by several other studies.^{8,9,11} In one prospective study of 34 patients, 94% of patients were overweight and 70.5% were obese.⁹

Another study of 50 women with IIH showed that 26 had IIH recurrence.² These patients had a greater BMI at the time of recurrence compared to BMI at diagnosis. In contrast, patients without recurrence demonstrated stable weights, while patients with recurrence had a 6% weight gain, suggesting that even moderate weight gain might be a risk factor for recurrence.²

Similar to the Western literature, the publications on IIH from GCC also show that obesity was the major risk factor contributing to the cause of IIH. A retrospective study of 40 Omani patients diagnosed with IIH showed that 60% of female patients were obese. ¹⁴

Another study in Saudi Arabia included 99 patients who were all Arab by ethnicity and ages between 12–48 years. This study showed that 80% of patients were obese.²¹ Mezaal

Table 1. Modified Dandy criteria.

Modified Dandy criteria

- 1. Symptoms, if present, and signs representing increased ICP or papilledema
- 2. Documented elevated ICP measured in the lateral decubitus position
- 3. Normal CSF composition
- 4. Normal MRI or contrast-enhanced CT for typical patient and MRI and MRV for all others
- 5. No other cause of increased ICP

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Table 2. Incidence of IIH in general population, women and obese women.

Country	Incidence	Incidence in women	Incidence in childbearing women	Incidence in obese women
US/lowa ¹⁶	0.9/100,000		13/100,000 > 10% ideal body weight	19.3/100,000 20% ideal body weight (childbearing)
US/Louisiana ¹⁶	1.07/100,000		14.85/100,000 > 10% ideal body weight	•
US/Minnesota 15	0.9/100,000	1.6/100,000	3.3/100,000	7.9/100,000
UK/Sheffield ¹⁸	1.56/100,000	2.86/100,000		11.9/100,000
Libya/Benghazi ¹⁷	2.2/100,000	4.3/100,000	12/100,000	21.4/100,000
Oman/South Sharaqiah 14	2.18/100,000	3.25/100,000	4.14/100,000	
Israel ²⁰	2.02/100,000	3.17/100,000	5.49/100,000	

Table 3. Estimated overweight (BMI $\geq 25 \text{ kg/m}^2$) and obesity (BMI $\geq 30 \text{ kg/m}^2$) prevalence, males and females, aged 15+, WHO estimates for 2010.³⁹

Region	Country	Overweight Male	Overweight Female	Obese Male	Obese Female
Americas	US	80.5	76.7	44.2	48.3
	Canada	66.9	59.5	25.5	25.7
	Mexico	73.7	73.0	30.1	41.0
Western Pacific	Australia	75.7	66.5	28.4	29.1
	New Zealand	73.9	74.2	28.9	39.9
Europe	UK	67.8	63.8	23.7	26.3
	Italy	55.0	40.0	14.4	13.7
	Belgium	54.1	42.9	14.8	10.7
	France	48.0	36.9	9.0	7.6
	Germany	67.2	57.1	22.9	22.1
Middle East: GCC	UAE	66.9	71.6	24.5	42.0
	Kuwait	69.5	80.4	29.6	55.2
	Bahrain	60.9	69.5	21.2	37.9
	Qatar	59.5	65.9	18.7	31.6
	Saudi Arabia	63.1	65.9	23	36.4
	Oman	43.4	50.8	7.7	17.0
Middle East	Jordan	57.5	65.4	19.6	37.9
	Syria	50.4	59.6	12.4	24.6
	Lebanon	51.7	56.7	14.9	27.4
	Libya	50.8	59.8	12.7	24.9
	Iraq	42.4	53.6	8.3	19.1
	Iran	48.5	60.2	10	29.5
	Israel	59.4	59.3	17.9	25.9
	Tunisia	42.8	61.4	7.7	32.6
	Yemen	24.6	32.2	2.0	6.2

and Sadaah et al. reported on 50 IIH patients from Dubai (UAE) and again obesity was the most commonly associated risk factor. Two studies conducted in Israel published in 2001 and 2014 by the same authors showed an increased percentage of obesity of 57.2% and 83.4%, respectively, as a major risk factor for IIH. 19,20

The pathophysiological mechanism of obesity in IIH remains unclear. Several hypotheses however include metabolic and hormonal dysregulation. Desity may raise intra-abdominal pressure which may increase pleural pressure and cardiac filling pressure leading to increased intracranial venous pressure and elevated ICP. Despite the major role of obesity in causing IIH, rarely non-obese patients of both genders also may develop the syndrome of IIH. A recent study showed that 4% of patients of both genders with IIH at the time of diagnosis were of normal weight.

IIH is uncommon in children. Interestingly, there is less predilection for obese girls in prepubertal children; however, the rate of obesity and gender predilection in post-pubertal children is similar to that in adult IIH population. In a retrospective study of 12 children with IIH, obesity was noted in 75% of patients and 100% in children above 12 years. Similarly, a retrospective study done in Israel reported no association between obesity and IIH in prepubertal children but their asso-

ciation more pronounced in the pubertal age group which is similar to the adult population with IIH.²³ In this study, 59% of involved children with IIH were overweight or obese. This study also showed the male predominance in the prepubertal group and female predominance in the pubertal group. While in another study conducted in Oman, thirteen patients of 40 were children below the age of 15, all of them were non obese. 14 This finding needs further evaluation to explore any other unidentified risk factor contributed to high incidence of IIH in Omani children. Being overweight or obese has an important role in the recurrence rate of IIH in the pediatric age group. A cohort study of 43 children with IIH showed that the risk of IIH recurrence was found five fold in overweight or obese children. 12 There was no available published literature in GCC or other Middle East countries about IIH in the pediatric age group and its associated risk factors.

IIH in men is rare. Only 9% of IIH patients in a recent large series were male. 6

Affected men have a similar BMI when compared with affected women, but are, on average, about a decade older than women at the time of presentation.⁶ In contrast, obesity is not as significant of a risk factor in men as it has been reported by available published studies in GCC but the study numbers are limited.^{10,14}

Clinical presentation

Patients with IIH typically present with symptoms and signs of elevated ICP. Headache is the most common presenting symptom reported by IIH patients, occurring in more than 90% of cases in most studies. ^{15,24,25} Some patients have accompanying neck stiffness or retrobulbar pain, the latter sometimes exacerbated by eye movements. Similar findings were reported by studies performed in GCC where 100% of involved patients in Oman, 97% in Saudi Arabia and 98% in Dubai (UAE) presented with headache. ^{10,14,21}

Many IIH patients are awakened by headache and they often suffer from daily headache. 25 Other symptoms may include transient visual obscurations (TVOs), blurred vision, recognition of enlarged blind spot or other visual field loss, diplopia (due to non-localizing sixth nerve palsy), and pulse-synchronous tinnitus (PST). Vision loss in IIH is usually due to papilledema and secondary optic neuropathy. Almost all patients with IIH have papilledema (although it may be absent). When present the papilledema is usually bilateral and symmetric, but can be slightly asymmetric or unilateral in about 10% of patients.²⁶ Visual acuity typically remains normal in the early stages of papilledema. The visual field defects are typically nerve fiber in character (or an enlarged blind spot). This peripheral vision loss is typically insidious and many patients are unaware of minor deficits because central vision is usually spared until late. An uncommon, but well-recognized fulminant presentation can occur, in which patients develop acute and severe vision loss over days.³⁸ Focal neurological deficits other than vision loss and sixth nerve palsy are not associated with IIH.

Diagnostic evaluation, clinical management and treatment

The initial evaluation of a patient with suspected IIH should consist of complete ophthalmic and neurologic examinations, including formal visual field testing. Patients with IIH should undergo magnetic resonance imaging (MRI) with and without contrast, which is preferred over computed tomography (CT) scanning with contrast, to rule out tumor, hydrocephalus, and meningeal lesion. Magnetic resonance venography (MRV) should be considered to assess for venous sinus occlusion especially in atypical IIH (e.g., men, thin patients, elderly).²⁸ Common characteristic MRI findings in IIH include an empty sella, flattening of the posterior globe, and enlarged optic nerve sheaths. Stenosis or narrowing of the distal transverse sinus-sigmoid sinus junction is common in IIH and it remains controversial as to whether this is contributory, coincidental with, or causal of the increased ICP in IIH. If neuroimaging is normal, a lumbar puncture (LP) is necessary to document elevated opening pressure and to rule out CSF infectious, neoplastic, or inflammatory causes. Assessment of optic nerve function (e.g., testing of visual acuity, color vision, pupillary reactions, formal visual fields) and funduscopy should be done at initial and follow up visits.

Treatment of IIH patients depends on their symptoms and vision status.

Asymptomatic patients with normal vision and minimal papilledema can be monitored frequently for the development of symptoms or vision loss. If headache is controlled with analgesic and no vision loss, patients may be managed

conservatively. The treatment of IIH patients can be divided into medical treatment and surgical treatment. The main stay of medical treatment is weight loss. All overweight and obese patients are strongly encouraged to lose weight. Improvement in IIH has been reported following a weight reduction diet and gastric bypass surgery. 42,43 IIH patients with mild to moderate vision loss typically require medical therapy. Acetazolamide, a carbonic anhydrase inhibitor, is the first-line medication in these instances. The recently completed IIH treatment trial (a major recent multi-center, randomized, double-blinded, placebo-controlled study) showed that weight reduction coupled with acetazolamide was a safe and effective treatment for IIH. The use of acetazolamide with a low-sodium weight reduction diet, compared with diet alone, resulted in modest improvement in the visual field function in the IIHTT.44

Patients with intractable headache, severe vision loss at presentation or progressive vision loss despite maximum medical management, may require surgical intervention. The primary surgical options are optic nerve sheath fenestration (ONSF) or a CSF diversion procedure (e.g., lumboperitoneal shunt (LPS) or ventriculo-peritoneal shunt (VPS)). No significant differences were found in the evaluation, assessment, management and treatment of IIH patients in studies performed in GCC versus the Western literature but the effect of weight reduction alone was not studied prospectively in the GCC studies. 10,21 In contrast, 35 of 40 patients in Oman study underwent CT scan alone and 5 patients had MRI and none had an MRV. 14 This may contribute partly to high incidence of IIH in this study as CT scan is not considered sufficient to make the diagnosis of IIH in the Western literature.

Outcome

Vision loss is the main long-term complication of IIH. Patients with mild to moderate vision loss tend to recover vision following maximum medical therapy. Papilledema in treated cases usually resolves completely over weeks or months but many patients are left with some residual disc elevation or mild gliosis or optic atrophy. Patients with severe vision loss at presentation or who fail maximum medical therapy may require surgery and these patients often have some potential for residual visual acuity and/or visual field defects. Rarely, cases act in a malignant fashion (i.e., fulminant IIH) and seem recalcitrant to medical and surgical therapy and result in severe secondary optic atrophy.

In a study of 57 patients, 24.6% of patients had severe visual impairment about 5–41 years after the initial diagnosis. ³⁰ Visual impairment was also reported in 13% of patients' eyes at initial visit with no significant changes at final visit and 4% of patients became blind in both eyes in one study. ²⁴ Comparing these findings with findings in the available Middle East studies of IIH, the percentage of final visual impairment was similar. One third of patients involved in the retrospective study in Saudi Arabia had decreased visual acuity, 19.2% were visually impaired, and 2% were blind at initial presentation. ²¹ Following surgical or medical therapy 87% of all patients had excellent outcome. At late assessment 13.1% were visually impaired and 2% were blind. 20% of patients in study performed in Libya had moderate to severe vision loss which did not correlate with any specific risk factor. ¹⁷

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These findings suggest that there is no difference in the visual outcomes in Arab populations with IIH. In contrast, one study from Dubai (UAE) reported an excellent outcome in 95.2%. ¹⁰ There are some demographic factors affecting the prognosis. Large Western studies suggest that men and black (African-American) patients have a worse visual prognosis than women and non-black patients, respectively, with IIH. Although race does not seem to directly influence the incidence of IIH, race may be an important determining factor of a patients' visual prognosis. IIH in some studies was worse in black patients compared with whites living in the US, 33 and was worse in white US IIH patients compared with white French IIH patients. 34 There was no similar racial studies done for IIH in the Middle East, and the demographics of race differ significantly in the GCC compared with the US. The demographics of the GCC, however, are rapidly evolving with expatriates from the Western world (Europe, North America, Australia/New Zealand), Asia (China, India, Pakistan, Bangladesh, and the Philippines), and Africa.

Although men develop IIH less frequently than women, their visual prognosis may be worse, perhaps because they have less prominent headaches to alert them to the problem.⁶ Additionally, in a more recent study, increasing degrees of obesity were associated with an increased risk of severe vision loss, suggesting that very obese IIH patients should be closely monitored for progression of visual field loss.²⁷ Other underlying conditions which may predispose to a worse visual outcome include older age, high myopia, anemia, hypertension and uremia. The role of these specific risk factors has not been studied in detail in the GCC and other Middle East countries.

Recurrence can occur, and rarely some patients with IIH develop a chronic form requiring years of medical treatment. Kesler et al. reported almost 40% recurrence rate of IIH over a mean observation period of 6.2 years. In a recent retrospective study of 20 patients who were followed up for over 10 years, three patients had recurrence about 12–78 months after the initial resolution. A further six patients experienced delayed worsening about 28–135 months after an initial stable course. Eight of 30 Omani patients who were medically treated had recurrence after one year and six of all patients experienced chronic course. If Since delayed worsening and recurrence occur, patients with IIH should be kept under long-term follow up, especially patients having risk factors of worse visual prognosis.

Conclusion

IIH represents an increasing burden to public health as well as clinical practice especially in countries experiencing epidemic obesity, such as the GCC. For the most part, the available evidence suggests that the clinical findings, evaluation, management, treatment, and prognosis of IIH in the GCC are similar to the Western presentation of IIH. The etiology of increased ICP in IIH is unclear and remains a topic of much interest and continued research. The incidence in the general population of the Middle East countries is higher than in Western countries, and it is higher in obese females. Obesity is the major risk factor in occurring and recurrence of IIH and is associated with an increased risk of severe vision loss.³⁷ Identification of patients at high risk for irreversible vision loss, such as black (African–American) patients, men,

and patients with fulminant IIH may help to determine the best risk stratified management approaches and refine individualized treatment and follow-up strategies.²⁹ Many questions remain unanswered about IIH and other risk factors in the Middle East population due to lack of controlled studies and the changing demographics in the GCC. Further studies are necessary to determine if IIH in the GCC should be treated the same or differently than in the western literature.

Conflict of interest

The authors declared that there is no conflict of interest.

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