The incidence of idiopathic intracranial hypertension in Israel from 2005 to 2007: results of a nationwide survey

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Background and purpose: Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a disorder related to increased intracranial pressure without clinical, laboratory or radiological evidence of an intracranial space occupying lesion or cerebral sinus vein thrombosis, predominantly affecting obese women of childbearing age. Our aim was to determine the incidence and clinical features of IIH in Israel.

Methods: In a cross-sectional study, all medical records of patients discharged from the hospital with a primary diagnosis of IIH during 2005–2007 were reviewed.

Results: Four hundred and twenty-eight patients with a new onset of IIH were diagnosed. The average annual incidence rate was 2.02 per 100 000 with an incidence of 3.17 per 100 000 for women and 0.85 per 100 000 for men. The incidence rate in females of childbearing age (18–45) was 5.49 per 100 000. The female to male ratio for >17 years old was 6.1:1 (252 females and 41 males) and 2.1:1 (60 females and 28 males) for ages 11–17. Obesity was documented in 83.4% of patients. Body mass index (BMI) data were available for 159 (37.1%) patients; of these, 59.1% had a BMI ≥ 30.

Conclusion: The incidence of IIH in Israel has increased during the last decade. This finding could be related to the increasing rates of obesity. The association of IIH and obesity should be further explored especially with regard to the effect of weight reduction for primary prevention.

Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri (PTC), is a disorder related to increased intracranial pressure without clinical, laboratory or radiological evidence of an intracranial space occupying lesion or cerebral sinus vein thrombosis, predominantly affecting obese women of childbearing age [1–3].

The association between obesity and IIH is well established; >90% of women and >60% of men who suffer from this disorder are obese [2–4]. The annual incidence of IIH in the general population has been estimated as 1–2 per 100 000 [2,5,6]. However, the incidence has risen to 3.5–12 per 100 000 in women aged 20–44 years, and to 7.9–21 per 100 000 amongst obese women in the same age group [3–5].

Idiopathic intracranial hypertension is relatively uncommon in men, with reported female to male ratios of 4.3:1 to 8:1 [3,7]. A recent large series confirmed that only about 10% of IIH patients are men [8]. Despite a high predilection in obese young women, IIH can occur in children, older adults, and in non-obese persons of either sex [6,9,10].

In 2001, our study relating to the incidence of IIH in Israel was published [5]. Subsequently, during the last decade, a rise in obesity has been documented worldwide. Since obesity is the only known risk factor for the development of IIH, here the incidence of IIH in the Israeli population from 2005 to 2007 was studied and whether the incidence rate of IIH had risen in our population was examined.

Methods

In Israel, patients with suspected IIH are routinely hospitalized in tertiary hospitals with neurology departments or in medical centers with a neuro-ophthalmology
unit for further evaluation (Appendix). All the medical records departments in Israel at the time of the study were computerized. Lists of all patients discharged from the hospital with a primary diagnosis of IIH or PTC (ICD9 code 348.2) during 2005–2007 were generated. The medical records of all these patients were reviewed. Data on age at onset of symptoms, gender, population group (Jews or Arabs), country of birth, height, weight, body mass index (BMI), comorbidities, imaging reports and results of lumbar puncture were collected. Only cases in which the primary diagnosis of IIH was based on the modified Dandy criteria [1,4] and only newly diagnosed patients were included in the study. Patients with IIH without papilledema (normal optic disc) were ascertained but not included in the analyses. Patients with BMI > 30 were considered obese. When BMI was unavailable, the physician’s diagnosis of obesity was used.

The incidence of IIH in obese females and males aged 18–45 was calculated by dividing the number of obese patients in this age group by the estimated number of obese individuals in the Israeli population of the same age. The denominator was the number of individuals aged 18–45 (data from the Central Bureau of Statistics) multiplied by the prevalence of obesity in this age group [data published by the Israeli Center for Disease Control (Health in Israel)], performed separately for males and females.

The study was approved by the Institutional Review Board Committee in each hospital.

Statistical analysis

Incidence rates for IIH were calculated as follows: numerator, all newly diagnosed patients with IIH during 2005–2007; denominator, the average Israeli population for those years as published by the Central Bureau of Statistics. Age, gender and population specific rates were calculated. A comparison between characteristics of symptomatic patients and asymptomatic patients was performed using the chi-squared test and the Student’s t test when applicable. Comparisons between the age of onset, signs and symptoms of obese patients and non-obese patients were performed using the Student’s t test for continuous variables and the chi-squared test for categorical variables. For this comparison, only patients with a documented BMI were included. Analysis was performed separately for patients > 17 years and those ≤ 17 years.

Results

Data were collected from 19 medical centers including all hospitals with a neurology ward (except for a very small hospital that referred patients with IIH to a tertiary medical center nearby) and those with a neuro-ophthalmology unit.

During 2005–2007, 919 patients were diagnosed with IIH; 491 did not meet the Dandy criteria or the first diagnosis was made prior to 2005. During these years, 428 patients experienced a new onset of IIH: 149 patients in 2005, 131 in 2006 and 148 in 2007. The total Israeli population for these 3 years was 21 163 900. The average annual incidence rate was 2.02 per 100 000 [95% confidence interval (CI) 1.83–2.21]. Incidence rates by population group, gender and specific age groups are shown in Table 1. No differences were shown in the incidence between Jews and Arabs and between different ethnic groups amongst Jews. Females had significantly higher rates compared with males. The highest incidence rate was observed in females of fertility age (18–45 years). In the young age group, females 11–17 years had significantly higher rates compared with males (4.93 vs. 2.19 per 100 000 respectively, $P < 0.001$).

A majority of cases (339, 79.2%) were females (female to male ratio 3.8:1). In patients > 17 years, the female to male ratio was 6.1:1 (252 females and 41 males), and 2.1:1 (60 females and 28 males) in patients aged 11–17. The mean age at diagnosis was 25.39 ± 13.04. Age of diagnosis was significantly higher in females compared with males (26.40 ± 12.25 and 21.6 ± 15.20, $P = 0.001$). This was also found in the younger age group (12.75 ± 3.71 in females and 10.42 ± 4.94 in males, $P = 0.006$) but not in the older group (> 17), where age at diagnosis was higher in males than females (34.62 ± 12.48 and 31.17 ± 10.50 respectively, $P = 0.06$).

Most patients (407/428, 95.1%) were symptomatic. In both adults and adolescents, the most common symptom was headache (81.8% and 80.7%, respectively). Amongst adults, symptoms included blurred vision (50.9%), nausea and vomiting (25%), double vision (13%), dizziness (8%) and tinnitus (7.3%). Amongst adolescents, nausea and vomiting (32.6%), blurred vision (28.9%), double vision (15.6%) and dizziness (11.1%) were the most common complaints.

Diagnosis of IIH was made inadvertently following a routine ophthalmological examination in 21 (4.9%) asymptomatic individuals. Patients > 17 years were significantly more often symptomatic compared with the younger age group (odds ratio 3.80, 95% CI 1.54–9.09, $P = 0.001$). Females were significantly more often symptomatic compared with males (odds ratio 3.06, 95% CI 1.25–7.52, $P = 0.01$); 80.3% of symptomatic patients were females compared with
Table 1 Average annual incidence of idiopathic intracranial pressure in Israel during 2005–2007 (per 100 000)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Population size</th>
<th>Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>428</td>
<td>21 163 900</td>
<td>2.02</td>
</tr>
<tr>
<td>Population group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jews</td>
<td>339</td>
<td>16 978 400</td>
<td>1.99</td>
</tr>
<tr>
<td>Arabs</td>
<td>89</td>
<td>4 185 600</td>
<td>2.12</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤17 years</td>
<td>123</td>
<td>7 041 500</td>
<td>1.75</td>
</tr>
<tr>
<td>&gt;17 years</td>
<td>293</td>
<td>14 123 200</td>
<td>2.07</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>89</td>
<td>10 457 800</td>
<td>0.85</td>
</tr>
<tr>
<td>Females</td>
<td>339</td>
<td>10 706 100</td>
<td>3.17</td>
</tr>
<tr>
<td>Males 0–10</td>
<td>20</td>
<td>2 333 200</td>
<td>0.86</td>
</tr>
<tr>
<td>Females 0–10</td>
<td>27</td>
<td>2 214 900</td>
<td>1.22</td>
</tr>
<tr>
<td>Males</td>
<td>28</td>
<td>1 277 300</td>
<td>2.19</td>
</tr>
<tr>
<td>11–17 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females 11–17 years</td>
<td>60</td>
<td>1 216 000</td>
<td>4.93</td>
</tr>
<tr>
<td>Males 18–45 years</td>
<td>33</td>
<td>4 163 500</td>
<td>0.79</td>
</tr>
<tr>
<td>Females 18–45 years</td>
<td>227</td>
<td>4 134 200</td>
<td>5.49</td>
</tr>
<tr>
<td>Obese males 21–45 years (estimate)</td>
<td>24</td>
<td>549 948</td>
<td>4.36</td>
</tr>
<tr>
<td>Obese females 21–45 years (estimate)</td>
<td>127</td>
<td>392 550</td>
<td>32.35</td>
</tr>
<tr>
<td>Country of origin (for Jews)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>89</td>
<td>5 621 700</td>
<td>1.58</td>
</tr>
<tr>
<td>Europe and America</td>
<td>104</td>
<td>6 088 900</td>
<td>1.71</td>
</tr>
<tr>
<td>Asia</td>
<td>53</td>
<td>2 073 600</td>
<td>2.55</td>
</tr>
<tr>
<td>Africa</td>
<td>56</td>
<td>2 576 700</td>
<td>2.17</td>
</tr>
</tbody>
</table>

57.1% of asymptomatic patients. No significant association was found between population group and symptoms \((P = 0.2)\).

In 357/428 patients (83.4%) a reference to obesity appeared in the medical records; 48.1% were described as ‘obese’. Information on BMI was available in 159 (37.1%) patients only; of these, 59.1% had a BMI ≥ 30.

Time to diagnosis was significantly longer for those ≤17 \((145.0 \pm 259.9 \text{ days})\) compared with the adult group \((96.4 \pm 170.3)\) \((P = 0.03)\). No statistical difference was found in opening pressure between females and males \((368.93 \text{ and } 349.24 \text{ mm respectively, } P = 0.08)\) and between the pediatric group and the adult group \((362.4 \text{ vs. } 349.2 \text{ mm, } P = 0.22)\).

Eighteen patients (4.2%) were diagnosed with IIH without papilledema (signs of increased intracranial pressure, normal neuroimaging and high opening pressure with normal constituents). Seven patients (38.9%) were ≤17 years old.

Discussion

In this nationwide cross-sectional study, clinical and demographic information on patients with IIH was obtained from 19 medical centers including all hospitals with a neurology ward (except for a very small hospital that referred patients with IIH to a tertiary medical center nearby) and those with a neuro-ophthalmology unit in Israel. The average annual incidence rate in the general population was 2.02 per 100 000, two and half times higher than the rate found in Israel in 1998–1999 \([5]\). This increase was observed in females (1.82 per 100 000 in 1999 to 3.17 in the present study) and was much more profound in males (0.1 per 100 000 to 0.85 in the present study). However, since the present study and the previous one differ in their methodology, there are some concerns as to the magnitude of the difference. Both studies were conducted in all the relevant medical centers at the time of the study. In 1998–1999 there were 15 medical centers and in 2005–2007 three new centers were opened. In both studies these centers served the whole population. The definition of IIH was similar in both studies. The main difference between the studies is the method by which patients were ascertained. In 2005 all medical records departments were already computerized, which allowed patient ascertainment through the ICD9 code of the primary diagnosis. The study conducted in 1998–1999 relied on the reporting by chairmen of the relevant departments and could therefore have resulted in some underestimate of the true incidence of IIH. However, since the diagnosis of IIH is not common and on average there were only about eight patients per year in each medical center under-reporting is unlikely to explain a difference of 250%. Our findings corroborate previous studies showing that the highest incidence rate of IIH was amongst obese females of childbearing age \([5,9,11,12]\) and that females were significantly more often symptomatic than males \([13]\).

Noteworthy in the present study is the high incidence found in adolescents: 1.75 per 100 000 for ≤17 years old. However, when age and gender were considered, the incidence rate was 2.19 per 100 000 in males and 4.93 per 100 000 in females aged 11–17. Lower rates were reported in other studies. In Canada, the incidence rate was 0.9 per 100 000 in children and adolescents aged 2–15. When age and gender were considered, a higher incidence was found in females aged 12–16, 2.2 per 100 000 \([14]\).

A recent German study found that the annual incidence for adolescents ≤17 years was 0.5 per 100 000 \([15]\). Female to male ratio for IIH in prepubertal IIH patients was 1.4. After puberty, a distinct female
predominance emerged (2.2:1) as reported in other studies [16–18].

Obesity (identified by BMI) was observed in 59% of the study group. No significant differences were found between males and females. Information on BMI was available for only 37% of the patients, and this makes it difficult to draw a firm conclusion regarding obesity as the main contributor to this increase in incidence. However, our findings are in agreement with other studies (Table 2) [19–26]. Over the last decade, the prevalence of obesity in western countries has more than doubled [13].

It is possible that the increase in the incidence rate in the present study is attributed to the increasing rates of obesity in Israel. In 2002, the self-reported prevalence of obesity in Israel was 12.2% in males and 12.8% in females, with an increase of 32.8% in males and 19.5% in females to 16.2% and 15.3% in 2010 [27]. Our figures are generally higher than those reported in other countries (Table 2). The delay in diagnosis of IIH observed in the present study in subjects ≤17 years underlines the need for increased awareness of IIH in adolescents.

Since 1972, when Lipton and Michelson [28] reported the first case of IIH without papilledema, several authors have reported patients with headache and IIH without papilledema [29]. In our study, 4.2% were diagnosed with IIH without papilledema; of them 61% were >17 years old.

**Conclusion**

In conclusion, IIH is a serious condition strongly associated with obesity and can cause severe visual loss. The findings in the present study suggest an increasing incidence that could be related to the obesity epidemic. It is important to explore whether weight loss can prevent IIH in susceptible individuals.

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**Disclosure of conflicts of interest**

The authors declare no financial or other conflicts of interest.

**References**


<table>
<thead>
<tr>
<th>Country, year</th>
<th>Total</th>
<th>Female</th>
<th>Female/male</th>
<th>Females 18–45</th>
<th>Percent obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libya, 1986 [19]</td>
<td>1.7</td>
<td>3.6</td>
<td>1:0</td>
<td>10.3</td>
<td>74</td>
</tr>
<tr>
<td>USA, 1988 [3]</td>
<td>0.9   Iowa</td>
<td>–</td>
<td>8:1</td>
<td>3.5</td>
<td>67</td>
</tr>
<tr>
<td>USA, 1993 [20]</td>
<td>0.9   Louisiana</td>
<td>1.6</td>
<td>8:1</td>
<td>3.5</td>
<td>69</td>
</tr>
<tr>
<td>Libya, 1993 [21]</td>
<td>2.2   Minnesota</td>
<td>4.3</td>
<td>3.3</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Japan, 2000 [22]</td>
<td>0.03  –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>UK, 2001 [23]</td>
<td>0.51  –</td>
<td>0.86</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Israel, 2001 [5]</td>
<td>0.94, 0.57</td>
<td>1.82</td>
<td>14:1</td>
<td>4.02</td>
<td>57</td>
</tr>
<tr>
<td>Italy, 2004 [24]</td>
<td>0.28  –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Spain, 2007 [25]</td>
<td>5.4   –</td>
<td>9:1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK, 2011 [26]</td>
<td>1.56  –</td>
<td>2.86</td>
<td>14:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel (present study)</td>
<td>2.02</td>
<td>3.17</td>
<td>3.8</td>
<td>5.49</td>
<td>59</td>
</tr>
</tbody>
</table>

Table 2 Incidence rates of idiopathic intracranial pressure in various studies (per 100 000)


**Appendix**

**Participating centers (in alphabetical order) who allowed access to the data**

Assaf Harofeh Medical Center, Zerifin, Israel: Titler J, MD

Barzilai Medical Center, Ashkelon, Israel: Milo R, MD

Bnai Zion Medical Center Haifa, Israel: Weller B, MD

Carmel Medical Center Haifa, Israel: Meer J, MD

Edith Wolfson Medical Center, Holon, Israel: Lampel Y, MD

Emek Medical Center, Afula, Israel: Jabaly Habib H, MD

Hadassah University Hospital, Jerusalem, Israel: Ben Hur T, MD PhD, Kahana S, MD

Hillel Yaffe Hospital, Hadera, Israel: Carasso R, MD

Kaplan Hospital, Rehovot, Israel: Leiba H, MD

Meir Medical Center Kfar Saba, Israel: Klein K, MD

Rabin Medical Center, Petach Tikva, Israel: Kalish H, MD, Reich E, MD

Rambam Medical Center, Haifa, Israel: Shiler Y, MD

Rivka Ziv Hospital, Tzfat, Israel: Shahein R, MD

Shaare Zedek Medical Center, Jerusalem, Israel: Koren Lubezky, MD

Sheba Medical Center, Tel Hashomer, Israel: Chapman J, MD

Soroka University Medical Center, Be’er Sheba: Virigin I, MD

Tel Aviv Medical Center, Tel Aviv, Israel: Kesler A, MD

Western Galilee Hospital, Naharia, Israel: Gross B, MD

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