European Journal of Ophthalmology / Vol. 14 no. 1, 2004 / pp. 48-54

Idiopathic intracranial hypertension (pseudotumor cerebri): descriptive epidemiology, clinical features, and visual outcome in Parma, Italy, 1990 to 1999

A. CARTA[1], F. BERTUZZI[1], D. COLOGNO[2], C. GIORGI[3], E. MONTANARI[3], S. TEDESCO[1]

[1]Institute of Ophthalmology
[2]Institute of Neurology
[3]Neurology Clinic, University of Parma, Hospital of Fidenza - Italy

PURPOSE. *To ascertain the annual incidence rate and the clinical features, other than visual outcome, of idiopathic intracranial hypertension (IIH) in Parma, northern Italy.*
METHODS. *Neurologic care of people living in the Parma area is entirely provided by one private and two public hospitals. Medical records related to IIH were retrospectively reviewed for all Parma residents from 1990 through 1999.*
RESULTS. *Ten patients (8 women and 2 men) were identified as having IIH according to modified Dandy criteria. Their age ranged from 16 to 53 years with a mean of 36 years at diagnosis. The annual age-adjusted rate per 100,000 is 0.28 for the total population. For women in reproductive age, the annual incidence rate is 0.65/100,000. For overweight women in reproductive age, the annual incidence rate is 2.7/100,000.*
CONCLUSIONS. *The incidence rate found in this study is lower than the incidence reported in previous US and Libyan studies. A significant difference in overweight distribution is observed comparing percentage of body weight between US and Parma populations. As overweight and obesity are important factors contributing to IIH development, it is possible that their low percentage in the Parma population may, at least partially, explain the low IIH incidence observed. (Eur J Ophthalmol 2004; 14: 48-54)*

KEY WORDS. *Idiopathic intracranial hypertension, Pseudotumor cerebri, Epidemiology, Papilledema, Amaurosis fugax*

Accepted: November 23, 2003

INTRODUCTION

Idiopathic intracranial hypertension (IIH), also termed pseudotumor cerebri, is a syndrome of elevated intracranial pressure without clinical, laboratory, or radiologic evidence for a space-occupying lesion or hydrocephalus. The confirmed diagnosis of IIH requires 1) documented elevation of intracranial pressure; 2) a normal neurologic examination except for papilledema and possibly sixth nerve palsy, 3) absence of space occupying lesion or ventricular enlargement on computed tomography (CT) or magnet-

1120-6721/048-07$15.00/0

ic resonance imaging (MRI); and 4) a normal cerebrospinal fluid (CSF) composition (1-3). The symptoms of IIH are those typical of elevated intracranial pressure: pulsatile headache that may be precipitated by changes in posture, prolonged vomiting, pulsatile tinnitus, amaurosis fugax, blurred vision, and diplopia. The associated signs are papilledema and occasionally sixth nerve palsy. Any other focal neurologic sign should suggest a different diagnosis.

Several pathogenetic mechanisms have been suggested for IIH, including decreased CSF absorptive capacity, obstruction or impairment of intracranial venous drainage, cerebral edema, hypersecretion of CSF, and any increased cerebral blood volume, but to date there is no satisfactory pathogenetic explanation for this disease (4, 5). Many studies have emphasized the association of IIH with menstrual irregularities, pregnancy, oral contraceptive intake, hypo-hyperthyroidism (6, 7), hypervitaminosis A (8, 9), and with a wide spectrum of medical therapies (10-18). Lee et al have recently reported the association of sleep apnea syndrome and IIH in men in a retrospective noncomparative case series (19). However, potential risk factors have not been sufficiently evaluated by prospective and case-control studies. Two recent case-control studies could not confirm any of these associations except for obesity and a recent increase in body weight before the onset of symptoms (20, 21).

The main morbidity of IIH is visual field and visual acuity loss secondary to progressive optic neuropathy. Complete blindness and optic atrophy may occur if prolonged intracranial hypertension has been left untreated. The frequency of visual field loss and acuity loss with IIH is variable, but in one study field loss was noted in 77.5% of eyes using automated threshold perimetry (22). Visual acuity loss in IIH occurs in about 80% of eyes tested and legal blindness occurs in about 10% of patients (23). Systemic hypertension and recent weight gain have been reported to be significant risk factors for visual loss (24).

The hospital incidence reported in several large series suggests that IIH is a relatively rare disorder. At present there are few studies evaluating the incidence of IIH in a population (25-29). They reported an annual incidence per 100,000 of 1.0 to 2.2 for the total population, and 3.5 to 12.0 for women in the reproductive age groups; for those defined as obese (body mass index [BMI] > 26), the incidence rate increased up to 21.4. The reported female-to-male ratio was 8:1 in two studies. The epidemiologic studies mentioned have been performed in specific geographic areas (United States, Israel, and Libya), with a wide difference in IIH incidence rates among the populations examined. It is possible that such a difference is related to the high prevalence of obesity among females of the reproductive age group in the Lybia population, as postulated by Radhakrishnan et al (28). To our knowledge, there is only one report about IIH epidemiology in Europe (30). In this study performed over a 5 year period in Ireland, the incidence rate of IIH is significantly lower than rates reported in previous studies.

The purpose of our study was to ascertain the annual population-based incidence rate of IIH and to report the clinical features of incident cases diagnosed among the population of Parma, northern Italy, over a 10 year period (1990 to 1999).

METHODS

The population of Parma (approximately 400,000 at the 1999 census) provides an excellent resource for this epidemiologic study, because medical care of people living in this area is entirely supplied by two public hospitals (Parma and Fidenza) and one private clinic ("City of Parma" private clinic). These are the only establishments that may offer diagnostic and therapeutic options for people with neurologic problems. Even in cases for which final medical care has been offered elsewhere, patients with intracranial hypertension necessarily have been evaluated at the first visit in these hospitals.

For this study, diagnoses consistent with IIH were indexed for computer retrieval in the electronic medical charts storage system of each hospital, thus allowing access to the original medical records for a preliminary screening. In order to identify IIH cases, medical charts with the following diagnoses were reexamined: pseudotumor cerebri, IIH, papilledema, brain tumor, hydrocephalus, chronic tension headache, intracranial venous sinus thrombosis, and migraine.

Only patients whose data in the medical chart clearly satisfied the modified Dandy criteria were diagnosed as IIH. Furthermore, CSF opening pressure and BMI

TABLE I - AGE- AND SEX-SPECIFIC AVERAGE ANNUAL INCIDENCE RATES OF IDIOPATHIC INTRACRANIAL HYPERTENSION PER 100,000 POPULATION IN PARMA, ITALY, 1990 TO 1999

Age group, yr	Males		Females		Total	
	No.	Rates	No.	Rates	No.	Rates
0-14	0	0.00	0	0.00	0	0.00
15-24	1	0.508	1	0.534	2	0.521
25-34	0	0.00	2	0.581	2	0.318
35-44	0	0.00	2	0.731	2	0.355
45>	1	0.114	3	0.281	4	0.206
All age groups	2	0.124	8	0.425	10	0.28

calculation were reported for identified cases.

Follow-up data regarding visual status were available for all these patients; this included a complete neuro-ophthalmologic evaluation with visual field testing. Each patient performed both Goldmann and automated static perimetry at baseline. During the follow-up, each patient underwent automated static perimetry with 30-2 program when using Humphrey Visual Field Analyzer (Humphrey Instruments) or glaucoma full-threshold program when using the Octopus perimeter (Swiss Interzeag). Perimetry was performed every 3 months for the first year. For those patients with stabilized visual field after 1 year of therapy, perimetry was subsequently performed every 6 months.

To be considered a case, onset of symptoms had to have occurred in the decade between January 1, 1990, and December 31, 1999. Cases outside the county of Parma were not included in the study and only patients native of this area or living here for at least 5 years were evaluated for our purposes. Age- and sex-specific incidence rates were calculated by dividing the number of incident cases by the proper denominator, estimated from the 1999 decennial census of the population of Parma.

Obesity was defined as a BMI (weight in kilograms divided by the square of the height in meters) of 26 or more.

According to the Italian National Health Survey, 1990–91, 24.2% of women and 38.3% of men in northeast Italy (Parma area) have an excessive body mass related to their stature. These parameters were used to determine the proportion of obesity in the local population.

RESULTS

Incidence rates

From a total of 1353 medical records that were examined, 10 cases (8 women and 2 men) of IIH were identified in the Parma population. Their age ranged from 16 to 53 years. The mean age at diagnosis was 36 ± 12.1 years for women, and 35.5 ± 14.8 for men. Average annual incidence rates per 100,000 persons for IIH by age and sex are shown in Table I. The annual age-adjusted rate per 100,000 is 0.28 for the total population. The age-adjusted rates are 0.12/100,000/ year for males and 0.43/100,000/ year for females. The female-to-male ratio is 4:1. For women in reproductive age (15 to 44 years), the annual incidence rate is 0.65/100,000. For women defined as overweight (BMI > 26) in the reproductive age, the annual incidence rate is 2.7/ 100,000. Our data are compared with other epidemiologic studies on IIH in Table II.

Clinical features

Duration of symptoms prior to diagnosis varied from 20 days to 5 months, with a median of 30 days. Headache was present in all but one patient and papilledema was evident in all patients at first examination. Transient visual obscuration lasting few seconds and persistent blurred vision were reported in eight cases. Decreased visual acuity and diplopia were seen in three cases as initial, but not isolated, symptoms. Visual loss was never reported as the main complaint. Enlarged blind spot was observed in all cases, whereas significant constriction of the visual field was ev-

TABLE II - COMPARISON OF DATA FROM POPULATION-BASED STUDIES OF IDIOPATHIC INTRACRANIAL HYPERTENSION

Population	Benghazi Lybia (1986)	State of Iowa (1988)	State of Louisiana (1988)	Rochester, Minnesota (1992)	Benghazi Lybia (1992)	Northern Ireland (2001)	Israel (2001)	Italy (2003) Current study
Total population	1.5	0.9	1.1	0.9	2.2	0.5	0.57	0.28
Females population	3.6	-	-	1.6	4.3	0.9	1.82	0.43
Females 15-44 yr	-	3.5	-	3.3	12	-	4.02	0.65
Obese females, 15-44 yr	-	-	-	7.9*	21.4†	-	-	2.7 (1)
Obese females, 20-44 yr	-	19.3†	14.9‡	-	-	-	-	-

*Body mass index greater than 26; †Overweight more than 20%; ‡Obesity not defined

ident in three patients.

The CSF opening pressure in lateral decubit ranged from 500 to 620 mm CSF, with a mean of 558.3 ± 50.7 mm CSF. All cases had normal CSF composition.

Outcome of patients

All patients were treated with diuretics and severe weight reduction (approximately 6–10% of weight loss as suggested by Kupersmith et al (31) and Johnson et al (32), possibly within 1 month from diagnosis); in our series the weight loss has been calculated between 5 and 12 kg and was maintained for at least 3 months of follow-up. One patient had bilateral optic nerve sheaths decompression for progressive visual field deterioration. Another patient had lumbo-peritoneal shunting. Follow-up ranged from 2 months to 7 years, with a median of 7 months. Two patients (20%) had a recurrence during follow-up, developing a mild optic atrophy not involving the papillo-macular bundle.

Visual acuity was better than 20/32 in all patients when last seen, but peripheral visual field was moderately restricted in two cases, whereas diffuse reduction of sensitivity was observed in two other cases (MD 8.19 DB, CPSD 2.28 DB).

DISCUSSION

The patients in our study ranged in age from 16 to 53 years, with a mean age of 35 years. This age distribution is similar to that in other epidemiologic reports (25-30). The female preponderance and high frequency of obesity found in many previous studies were confirmed in our series, with a female to male ratio of 4:1.

The average crude annual incidence rates of IIH in Parma, northern Italy, per 100,000 persons are 0.25 for the total and 0.45 for the female population. For women in reproductive age (15 to 44 years) the annual incidence rate is 0.65/100,000, and 2.7/100,000 in women in the same age group with a BMI > 26. These incidence rates are significantly lower than those reported in previous studies (Tab. II). Our data are in accordance with hospital incidence reported in several large series, suggesting that IIH is a relatively rare disorder. Although the results of this study are based on a small group of patients, it achieved the requirements of an ideal epidemiologic study; namely, precise diagnosis, well-defined population denominator, long period of observation, and a virtually complete ascertainment of symptomatic patients.

As previously noticed by many authors and further confirmed in our study, IIH tends to be a disease of early female adulthood and recent weight gain or obesity seem to play a key role in this disorder. Such clinical features have been extensively reported in the literature in many retrospective or small case series. Although potential risk factors for the development of IIH need to be tested in large, randomized, prospective clinical trials, the characteristics of our patients are similar to those generally reported for IIH cases, with the exception of male patients; in fact, as in our series we include only two male cases, we are unable to draw any conclusion regarding particular features of IIH in men.

A peculiar aspect of our study is the high mean and relatively narrow range of CSF opening pressure. In the literature, we have found only two studies reporting

the mean CSF opening pressure of the patients (28, 33). In the study of Radhakrishnan et al (28) the mean reported is 399.2 ± 103.7 mm, with a range from 260 to 950. In the study of Celebisoy et al (33) the mean reported is 376.21 ± 41.9 mm, with a range from 200 to 900. These data are significantly lower than mean CSF pressure reported in our study. As Radhakrishnan et al and Celebisoy et al examined 81 and 62 patients, respectively, compared to our 10 cases, such a large number of patients could partially account for the difference observed. Including more cases probably would require investigating more mild IIH cases with CSF pressure closer to lower than higher levels, thus accounting for the lower mean reported by the other authors.

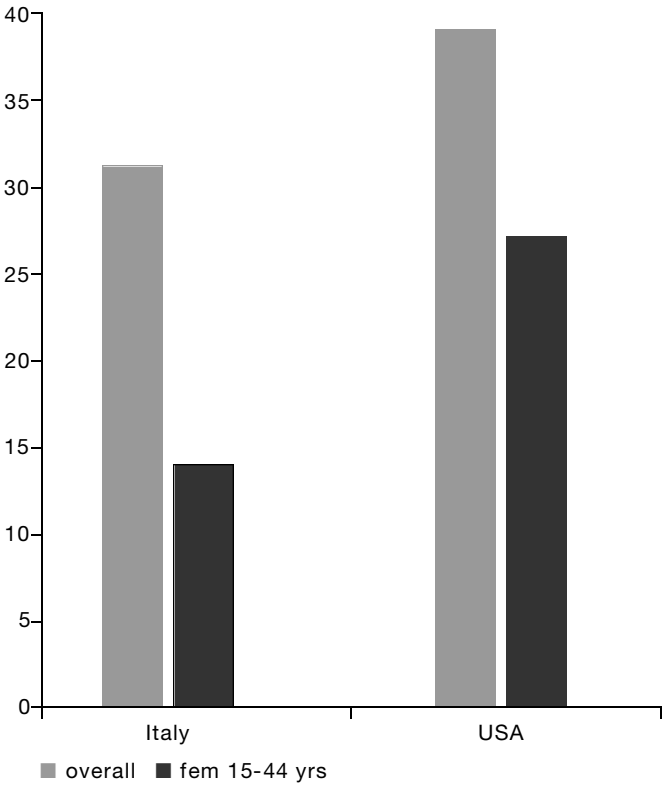
Several previous studies have emphasized vision loss as a frequent sequela of IIH. For example, severe visual deficits have been reported in up to 25% of hospital-based patients with IIH (24, 34). Twenty-two percent of the patients reported in the epidemiologic study from Iowa had visual loss, although the authors did not report the course of the visual deficit in detail (25). In our series, only two patients had very mild visual defects, not impairing the daily activity of such persons.

Median duration of symptoms prior to diagnosis in our series was 30 days (range 20 to 150 days). The Rochester series had the same median duration of symptoms, with a benign visual outcome for IIH patients. The duration of symptoms prior to diagnosis is not available for other population-based studies that reported a higher percentage of visual loss among their patients. In the Benghazi series, duration of symptoms before diagnosis was significantly longer, with a mean of 2.7 months (26). Moderate to severe vision loss occurred in 20% of these patients. As early diagnosis and therapy to reduce intracranial hypertension combined with a close follow-up for the detection of visual impairment have been shown to prevent (or, in some cases, reverse) visual loss, it is possible that poor visual outcome reported in several studies is related to the delay in the diagnosis and in the therapeutic intervention.

The most relevant finding of our study is the low percentage of IIH among the Parma population, compared to previous epidemiologic reports. Obesity and recent weight gain in the last 12 months are strongly associated with IIH development (20, 21). It is possible that the elevated incidence of IIH in countries such as Libya and Saudi Arabia is likely to be higher than in the US population because of the high prevalence of obesity among females of the reproductive age group; nevertheless, such authors did not provide obesity percentages in their studies (26, 29). According to these findings, a possible explanation of our low rates could be related to a low percentage of obesity in the Parma area among females in the reproductive age group. To support this hypothesis, we compared the percentage of overweight and obesity in Parma, Italy, with that reported in US adults. The prevalence of overweight and obesity in Italy was evaluated using data from the last Italian National Health Survey (1990–91), where prevalence was determined according to sex, age group, and geographic area (35).

These data are compared in Table III to the descriptive epidemiology of body weight in US adults reported in 1993 (36). In the overall Italian national sample, 31.6%

TABLE III - OVERWEIGHT AND OBESITY IN THE FEMALE POPULATION IN NORTHEASTERN ITALY (Parma area) AND UNITED STATES



of subjects are overweight and 6.5% are defined as obese; these percentages are slightly lower than US ones. The difference is more evident when related to some specific ethnic groups in the US study (whereas the Italian population remains more homogeneous). For example, whereas 37.7% of white US women have overweight/obesity, the percentage of black women with BMI > 26 is 64.8%. A more detailed analysis of these two studies reveals that among females in the reproductive age group (15 to 45 years old) a significant difference is observed in the percentage of overweight and obesity between the US and Italian population: whereas in the Italian sample (Parma area) 14.4% of persons have a BMI > 26, in the US study a doubling of this percentage is reported, with 27.5% of women aged 20 to 45 reported as overweight. As IIH is typically a disease affecting young, overweight or obese women, it is possible that the low percentage of overweight/obesity in our population can, at least partially, explain the low IIH incidence.

In summary, our study suggests that more investigations need to be aimed at considering the importance of weight gain in the pathogenesis of IIH. Future studies are also needed to prospectively evaluate potential risk factors in order to better understand IIH etiology and to optimize its treatment.

Reprint requests to:
Arturo Carta, MD
Neuro-Ophthalmology Service
Institute of Ophthalmology - University of Parma
Via Gramsci 14
43100 Parma, Italy
acarta@unipr.it

REFERENCES

1. Weisberg LA. Benign intracranial hypertension. Medicine 1975; 54: 197-207.
2. Ahlskog JE, O'Neill BP. Pseudotumor cerebri. Ann Intern Med 1982; 97: 249-56.
3. Smith JL. Whence pseudotumor cerebri? J Clin Neuro-Ophthalmol 1985; 5: 55-6.
4. Fishman RA. The pathophysiology of pseudotumor cerebri: an unsolved puzzle. Arch Neurol 1984; 41: 257-8.
5. Donaldson JO. Pathogenesis of pseudotumor cerebri syndromes. Neurology 1981; 31: 877-80.
6. Press OW, Landenson PW. Pseudotumor cerebri and hypothyroidism. Arch Intern Med 1983; 143: 167-8.
7. Roos RA, van der Blij JF. Pseudotumor cerebri associated with hypovitaminosis A and hyperthyroidism. Dev Med Child Neurol 1985; 27: 246-8.
8. Moskowitz Y, Leibowitz E, Ronen M, Aviel E. Pseudotumor cerebri induced by vitamin A combined with minocycline. Ann Ophthalmol 1993; 25: 306-8.
9. Sharieff GQ, Hanten K. Pseudotumor cerebri and hypercalcemia resulting from vitamin A toxicity. Ann Emerg Med 1996; 27: 518-21.
10. Korzets A, Rathaus M, Chen B, Bernheim J. Pseudotumor cerebri and nitrofurantoin drug intelligence. Clin Pharm 1988; 22: 345.
11. Sharma DB, James A. Benign intracranial hypertension associated with nitrofurantoin therapy. Br Med J 1974; 4: 771.
12. Cohen DN. Intracranial hypertension and papilledema associated with nalidixic acid therapy. Am J Ophthalmol 1973; 76: 680-2.
13. Mukherjee A, Dutta P, Lahiri M, et al. Benign intracranial hypertension after nalidixic acid overdose in infant. Lancet 1990; 335: 1602.
14. Walker AE, Adamkiewicz JJ. Pseudotumor cerebri associated with prolonged corticosteroid therapy. JAMA 1964; 188: 779-84.
15. Saul RF, Hamburger HA, Selhorst JB. Pseudotumor cerebri secondary to lithium carbonate. JAMA 1985; 235: 2869-70.
16. Campos SP, Olitsky S. Idiopathic intracranial hypertension after L-thyroxine therapy for acquired primary hypothyroidism. Clin Pediatr 1995; 34: 334-7.
17. Mayer-Hubner B. Pseudotumor cerebri from intranasal oxytocin and excessive fluid intake. Lancet 1996; 347: 623.
18. Price DA, Clayton PE, Lloyd IC. Benign intracranial hypertension induced by growth hormone treatment. Lancet 1995; 345: 458-9.
19. Lee AG, Golnik K, Kardon R, et al. Sleep apnea and intracranial hypertension in men. Ophthalmology 2002; 109: 482-5.
20. Ireland B, Corbett JJ, Wallace RB. The search for causes of idiopathic intracranial hypertension. A preliminary case-control study. Arch Neurol 1990; 47: 315-20.
21. Giuseffi V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri). A case-control study. Neurology 1991; 41: 239-44.

22. Wall M, George D. Visual loss in pseudotumor cerebri. Incidence and defects related to visual field strategy. Arch Neurol 1987; 44: 170-5.
23. Wall M, George D. Idiopathic intracranial hypertension. A prospective study of 50 patients. Brain 1991; 114: 155-80.
24. Corbett JJ, Savino PJ, Thompson HS, et al. Visual loss in pseudotumor cerebri: follow-up of 57 patients from 5 to 41 years and a profile of 14 patients with permanent severe visual loss. Arch Neurol 1982; 39: 461-74.
25. Durcan JF, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. Arch Neurol 1988; 45: 875-7.
26. Radhakrishnan K, Sridharan R, Ashok PP, Mousa ME. Pseudotumor cerebri: incidence and pattern in North-Eastern Libya. Eur Neurol 1986; 25: 117-24.
27. Radhakrishnan K, Ahlskog EJ, Cross SA, Kurland LT, O'Fallon M. Idiopathic intracranial hypertension (pseudotumor cerebri). Descriptive epidemiology in Rochester, Minn, 1976 to 1990. Arch Neurol 1993; 50: 78-80.
28. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE. Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci 1993; 116: 18-28.
29. Kesler A, Gadoth N. Epidemiology of idiopathic intracranial hypertension in Israel. J Neuroophthalmol 2001; 21: 12-4.
30. Craig JJ, Mulholland DA, Gibson JM. Idiopathic intracranial hypertension: incidence, presenting features and outcome in Northern Ireland (1991-1995). Ulster Med J 2001; 70: 31-5.
31. Kupersmith MJ, Gamell L, Turbin R, Peck V, Spiegel P, Wall M. Effects of weight loss on the course of idiopathic intracranial hypertension in women. Neurology 1998; 50: 1094-8.
32. Johnson LN, Krohel GB, Madsen RW, March Jr GA. The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). Ophthalmology 1998; 105: 2313-7.
33. Celebisoy N, Secil Y, Akyurekli O. Pseudotumor cerebri: etiological factors, presenting features and prognosis in the western part of Turkey. Acta Neurol Scand 2002; 106: 367-70.
34. Wall M, Hart WM Jr, Burde RM. Visual field defects in idiopathic intracranial hypertension (pseudotumor cerebri). Am J Ophthalmol 1983; 96: 654-69.
35. Pagano R, La Vecchia C. Overweight and obesity in Italy, 1990-91. Int J Obes 1994; 18: 665-9.
36. Williamson DF. Descriptive epidemiology of body weight and weight change in US adults. Ann Intern Med 1993; 119: 646-9.