Incidence and Prevalence of Dermatitis herpetiformis in a County in Central Sweden, with Comments on the Course of the Disease and IgA Deposits as Diagnostic Criterion

HARALD MOI

Department of Dermatology, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden

Moi H. Incidence and prevalence of dermatitis herpetiformis in a county in Central Sweden with comments on the course of the disease and IgA-deposits as diagnostic criterion. Acta Derm Venereol (Stockh) 1984; 64: 144–150.

In a defined area of 273 000 inhabitants in Central Sweden a total number of 125 patients with dermatitis herpetiformis (DH) were observed during the years 1974–1982. The incidence was calculated for the years 1943–1982 and was found to be 0.86–1.45 patients/100 000 inhabitants/year, which is in agreement with a report from Finland. However, the prevalence of DH in the area was 39.2 patients/100 000 inhabitants, which is much higher than previously reported. Spontaneous transient remissions of more than half a year duration were seen in 20% of the patients. At the end of the study, 16 out of 37 patients (43%) on normal diet used no dapsone because of no or minimal rash. Immunohistochemical demonstration of IgA-deposits at the dermoepidermal junction was found to be a good diagnostic criterion. Granular deposits were seen in all except one patient, also in those needing no dapsone. Five out of 6 patients with a granular-linear pattern were still alive at the end of the study, and all of them needed dapsone for control of the rash. *Key words: Bullous dermatoses; Dapsone-treatment; Gluten-free diet; Jejunal mucosal atrophy* (Received April 8, 1983.)

H. Moi, Department of Dermatology, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden.

Dermatitis herpetiformis (DH) is an uncommon disease, but the true incidence and prevalence are not known. Since the original demonstration of a connection between this itchy, bullous skin disease and coeliac disease (CD) (1), much attention has been paid to DH. The commonest way of confirming the diagnosis of DH has been to empirically assess the response of the rash to dapsone or sulfapyridine. However, the discovery of IgA-deposits in uninvolved skin, first described by van der Meer (2), highly increased the possibility to establish an exact diagnosis of DH (3).

For this reason, new studies on the occurrence of DH in a well defined population would be of interest. Unfortunately, such studies are sparse. The best documented publication on prevalence and incidence is from Finland and includes all DH-patients visiting the dermatological departments in Finland during a period of 3½ years (4). The present study includes all cases of DH observed and followed up in a defined area for the years 1974–1982. Biopsies from uninvolved skin were examined with direct immunofluorescence to establish the diagnosis. The incidence of the disease was calculated on the number of observed patients contracting DH per year up to 1982 as well as the prevalence of the disease at the end of 1982.

MATERIALS AND METHODS

Patients

125 patients, 84 males and 41 females were included in the study. There were two pairs of siblings. All the patients with a diagnosis of DH attending the Department of Dermatology, Örebro Medical Center

Hospital, were included, observed and followed up during the years 1974–1982. They were all living in Örebro County, a well defined area in Central Sweden. General practitioners and internists had been encouraged to refer all suspected DH-cases to the clinic. There are no dermatologists in the county working outside the dermatological department. The majority of the patients were seen 2–3 times a year in the outpatient department, most of them by the same physician. Some of the patients had been seen in the clinic since the dermatological department was founded in 1944.

Diagnosis

Up to 1974, the diagnosis was based on typical clinical features (3), and on the response of the rash to dapsone or sulfapyridine. In addition, biopsies from skin lesions were taken from most of the patients and routine histopathological examination was carried out. A subepidermal blister and presence of papillary microabscesses with predominant neutrophils were regarded as positive. Some patients were given potassium iodide orally in order to provoke a flare up of the rash (5).

Direct immunofluorescence (DIF)

Skin biopies were taken under local anaesthesia with a 4 mm punch (Stiesel Laboratorium GMBH) from uninvolved skin of the buttock as recommended by Fry & Seah (3), in a few cases also from perilesional skin. The biopsies were snap frozen in a mixture of CO_2 ice and absolute ethyl alcohol. They were stored at −70°C until cut into 4–5 μm sections in a cryostat microtome operated at −18°C. Following the principles recommended by Beutner et al. (6), the sections were airdried and stained with fluorescein isothiocyanate labelled antihuman IgG (the National Bacteriological Laboratory, Stockholm, Sweden) antihuman IgA, antihuman IgM and anti C'3 (Wellcome, England). The counter-staining described by Danielsson (7) was used by adding an equal part of undiluted lissamine rhodamin B labelled rabbit anti *S. aureus* globulin to the diluted fluorescein conjugates. The criteria for IgA-deposits given by Fry & Seah (3) were followed.

Since 1975 DIF has been used in our laboratory as a routine method for the demonstration of IgA-deposits. All DH-patients treated at the department up to that time were reexamined and biopsies for DIF taken. Subsequently DIF has been used as a screening test in all suspected new cases of DH, and as follow-up in patients on a glutenfree diet.

Small intestinal biopsy

In 56 patients jejunal biopsies just distal to the duodeno-jejunal junction were obtained under radiographic control with a Crosby capsule. After histopathological staining and examination the specimens were classified into 3 groups on the basis of the following criteria: *subtotal villous atrophy* (no or almost no villi, elongated crypts and extensive chronic inflammatory reaction in the lamina propria), *partial villous atrophy* (broad, often shortened villi, with slight crypt hyperplasia and slight or moderate inflammation), and *normal mucosa* (8).

Glutenfree diet (GFD) and dapsone treatment

Most of the patients were offered a GFD. Before starting the diet, patients were given detailed information by a dietitian. Subsequently, every patient on GFD had to call the dietitian every 3rd month in order to obtain prescriptions for glutenfree products almost free of charge. Most of the patients, even those not taking a GFD, were seen by a dietitian to assess the gluten intake at the end of the study. Less than 5 g gluten a day was judged as gluten restricted diet and no detectable gluten

Table I. *The incidence of dermatitis herpetiformis in Örebro County calculated on the number of patients contracting this disease up to 1982*

	Year of onset	Population in the county (mean)	Patients	(♂/♀)	Patients 100 000 inhabitants/ year
Group 1	Up to 1942		2	(1 : 1)	
Group 2	1943–52	241 000	24	(20 : 4)	1.0
Group 3	1953–62	256 500	22	(15 : 7)	0.86
Group 4	1963–72	269 000	39	(25 : 14)	1.45
Group 5	1973–82	274 000	32	(18 : 14)	1.17

intake was judged as GFD. Patients on dapsone treatment were reminded of the dose related side effects and were asked to gradually reduce this drug to the minimum acceptable dose.

Prevalence and incidence

The population data were collected from the Central Statistics Bureau, Örebro (9). In order to obtain the incidence data, all patients were placed into 5 groups according to the year in which they noticed their first skin symptoms (Table I). The incidence of DH was calculated using the mean number of inhabitants in the area during each decade after 1942. Only patients living in the county at time of onset of the rash were included in the incidence figures as denominator. All known DH-patients living in the county at the end of the study were included in the prevalence figures. Prevalence values are thus for the end of 1982.

RESULTS

Incidence

A total of 125 patients (84 males and 41 females) were diagnosed as having DH. There were 2 patients whose diseases began up to 1942 whereas 123 noticed their first skin symptoms during the 4 following 10-year-periods. Fourteen patients died and 4 moved from the county during the period of study but were included in the figures for calculating the incidence. Six patients were excluded since their rashes started before they settled in Örebro County. The incidence figures were thus calculated on 119 patients (Table I). The age at the onset of the rash in these 119 patients was 4–80 (mean 43.9 years in men and 39.9 years in women). The mean incidence for the years 1943–1982 was 1.12 patients/100 000 inhabitants/year, with the highest incidence in the period 1963–1972 in which 1.45 patients/100 000 inhabitants/year contracted the disease.

Prevalence

By the end of 1982 Örebro County had a total population of 273 000 inhabitants, and there were 107 known DH-patients, 70 males and 37 females (ratio 1.9 : 1), aged 21–89 (mean 58.3 years), who lived in the county. Based on these figures the DH-prevalence in the county was 39.2 patients/100 000 inhabitants or 1 patients/2 553 inhabitants (Table II). 17 000 (6.2 %) of the inhabitants in the county were born outside Sweden. One half of these immigrants were Finnish, the majority of the remaining were of Mediterranean origin. Three of the DH-patients were born in Finland, the rest in Sweden.

IgA deposits

Biopsies for DIF were taken from 121 of the 125 patients and IgA deposits were demonstrated in 120 of them (Table III). Such deposits were found in the 1st biopsy in 87 out of

Table II. *The prevalence of dermatitis herpetiformis calculated on the number of patients with this disease and still living in Örebro County by the end of 1982*

Population by the end of 1982		Patients	Patients/ inhabitants	Patients/ 100 000 inhabitants
Men	134 660	70	1 : 1 924	52.0
Women	138 468	37	1 : 3 742	26.7
Men ≥20 years	98 802	70	1 : 1 411	70.8
Women ≥20 years	104 118	37	1 : 2 814	35.5
All	273 128	107	1 : 2 553	39.2

91 patients (95.6%) diagnosed before 1975 and in 80% of those diagnosed after 1975. One patient in whom no IgA was demonstrated declined a 2nd biopsy. Six patients had granular-linear (GL) deposits of IgA (10) at the dermo-epidermal junction, but no case of homogeneous-linear (HL) deposits was seen.

Villous atrophy

Histopathological examination of small intestinal biopsies showed villous atrophy in 43 out of 47 patients (91%) who had not had GFD. Villous atrophy was demonstrated in another 2 out of 9 patients in whom the biopsies were taken after introduction of GFD. Small intestinal biopsy was taken from only 2 of the 6 patients with a GL-pattern of IgA deposits. Both of them had a subtotal villous atrophy.

Course of the disease

Fourteen out of 69 patients (20%) not treated by GFD for at least 2 years did not require dapsone for 0.5–18 years (mean 7.5 years). Some of them had recurrent mild rashes but needed no treatment during these periods of apparent remissions. At the end of the study, 16 out of 37 patients (43%) on normal diet needed no dapsone. Five of the 6 patients with GL-pattern were alive at the end of the study and all of them had to take dapsone for control of their rash. Two of them took a GFD since 3 and 8 years.

DISCUSSION

It is difficult to obtain the true incidence and prevalence figures of a particular disease in a population and the possibilities of errors are numerous (11). However, DH is regarded as a life long disease (12) and patients with this condition will not, as a rule, fail to seek medical advice (13). Örebro County has an exactly registered population, the medical standard is good, and probably all patients attending a doctor for suspected DH were referred to the dermatological department.

The incidence, defined as the number of patients contracting DH per year per 100000 inhabitants in the county, for a rare disease as DH might be heavily influenced if the population is small and the observation period short. The patients in the present study had contracted DH during a 40-year-period and the population was 270000 inhabitants. The yearly incidence for each of the 4 decades varied between 0.86 and 1.45 patients/100000 inhabitants/year. For the whole period the mean incidence per year was 1.12 and these findings are very similar to the incidence of 1.3 patients/100000 inhabitants/year reported from Finland (4). However, this high incidence in the Finnish investigation did only persist

Table III. *Collation of the results of direct immunofluorescence for IgA deposits in patients with DH*

	IgA deposits in skin biopsies			
Patients with DH	No.	1st biopsy	2nd or 3rd biopsy	Total
Diagnosed before 1974 and reexamined for IgA	1	87	3	91
Diagnosed 1974–1982 and screened for IgA	–	24	6	30
Total	1	111	9	121

during 3 years. A much lower incidence was reported from Great Britain (13), but this study was based on a postal survey. In contrast, Burrows (14) reported an incidence of 2.6 patients/100 000 inhabitants/year in Northern-Ireland, which is twice as much as in Finland (4) and in the present study. However, the figures reported by Burrows were obtained from a central diagnostic register and the diagnostic criteria were not discussed.

The prevalence, defined as the known number of DH-patients living in Örebro County by the end of the study, was found to be 39.2 patients/100 000 inhabitants. This is close to the theoretical figures of 39.8 and 49.3 patients/100 000 inhabitants based on the yearly incidence figures of 1.17 and 1.45 patients/100 000 inhabitants/year for the last 2 decades. (Mean age at the onset of DH was 43.9 in men and 39.9 in women. Life expectancy for a 44-year-old man in Sweden is 75 years and for a 40-year-old woman 80 years (9). With a male–female ratio of 1.9:1 the expected mean duration of the disease thus was 34 years.) The prevalence of DH in the present study is much higher than those reported by Reunala & Lokki (4) who found a prevalence of 10.4/100 000 inhabitants, with a minimum of 4.1 and a maximum of 16.3 in different provinces of Finland. The present prevalence figures are also much higher than those reported from Great Britain by Wyatt et al. (13) and by Marks (5).

It is obvious from the present study that the natural course of DH can vary to a large extent. At the end of the study there were 16 out of 37 patients (43 %) on a normal diet who had not needed dapsone for 0.5–30 years (mean 9.1 years). A high number (20 %) of the patients on a GFD had even had spontaneous remissions before the introduction of the diet. This could indicate that there were many mild cases included and that the DH-patients were followed up regardless of symptoms or not. This might explain a prevalence twice as high in Örebro County as of any province in Finland (4).

The demonstration of IgA deposits in uninvolved skin were found to be a good criterion for DH which confirms reports by others (3, 15, 16, 17, 18). Lack of IgA in the first biopsy in a patient with a typical picture and clinical diagnosis of DH cannot exclude a DH (15, 18). The duration of the disease might in this respect be important. In the present study IgA deposits failed in the first biopsy in only 4 % of the patients who were diagnosed up to 1974 and were reexamined but in 20 % of the patients who where diagnosed after this year and in whom DIF was used as a screening test. A possible reason could be a patchy distribution of IgA deposits in the skin in recently developed cases of DH.

The presence of granular IgA deposits seems to have a high specificity for DH (3). In more than 1800 skin biopsies screened for immunoglobulins in our laboratory during the last 8 years there were only 2 IgA-positive patients who were not considered to have DH. In one of these patients a second biopsy showed the presence of globular IgA deposits characterized as cytoid bodies (19). In the second patient examination of a 2nd and 3rd biopsy were negative for IgA. Both of them had a papular rash without dapsone response and without histopathological signs of DH. Seven patients who had had a diagnosis of DH for several years were negative for IgA in repeated biopsies. These patients were found not to have DH at a renewed clinical examination.

In the present study no case of homogeneous-linear IgA deposit was seen in any of the 120 IgA-positive patients. Only 10 cases HL IgA dermatosis were found in a Swedish multicentre study (20). This type of IgA deposits seems to be rare in Sweden compared with classical DH and with reports from other countries (10, 15, 21). Six of the patients in the present study had a granular-linear pattern of IgA deposits. It is noteworthy that 5 of these patients, still living at the end of the study, all required dapsone for control of their rashes. Clinically they did not differ from the patients with granular IgA deposits mainly in the dermal papillae. A higher consumption of dapsone in patients with GL pattern of IgA was even reported by Leonard et al. (10).

The close association between enteropathy and granular IgA deposits located to the dermal papillae (1, 10, 22) was confirmed in the present study. Jejunal mucosal atrophy was demonstrated in 85% of the patients in the first biopsy. Three patients with normal small intestinal mucosa in the first biopsy had biochemical signs of malabsorption. New biopsies taken 1–3 years later revealed partial to subtotal villous atrophy. Failure to demonstrate enteropathy in the first small intestine biopsy could be due to a patchy involvement of the gut (23).

The relation of enteropathy to the skin symptoms in DH is not known, but several investigations have shown GFD to be of benefit for the rash (12, 17, 22, 24). These studies were performed on selected DH-patients. Dietary studies of non-selected patients would, however, be of interest since 16 out of 37 patients (43%) on normal diet were in clinical remission at the end of the present study. Such investigations are now under way and will be reported separately.

ACKNOWLEDGEMENTS

I am indebted to all my colleagues in the dermatological department and to Prof. F. Schoenknecht, Prof. S. Jablonska and Ass. Prof. D. Danielsson for their helpful assistance, advice and criticism.

REFERENCES

1. Marks JM, Shuster S, Watson AJ. Small bowel changes in dermatitis herpetiformis. Lancet 1966; ii: 1280–1282.
2. Meer JB van der. Granular deposits of immunoglobulins in the skin of patients with dermatitis herpetiformis. An immunofluorescent study. Br J Dermatol 1969; 81: 493–503.
3. Fry L, Seah PP. Dermatitis herpetiformis. An evaluation of diagnostic criteria. Br J Dermatol 1974; 90: 137–146.
4. Reunala T, Lokki J. Dermatitis herpetiformis in Finland. Acta Derm Venereol (Stockh) 1978; 58: 505–510.
5. Marks JM. Dogma and dermatitis herpetiformis. Clin Exp Dermatol 1977; 2: 189–207.
6. Beutner EH, Nisengard RJ, Kumar V. Defined immunofluorescence: Basic consepts and their application to clinical immunodermatology. In: Beutner EH, Chorzelski TP, Beam SF, eds. Immunopathology of the skin, 2nd ed. New York, Chichester, Brisbane, Toronto: Wiley Medical Publication, J. Wiley & Sons, 1977: 29–75.
7. Danielsson D. The demonstration of N. gonorrhoeae with the aid of fluorescent antibodies. 5. A comparison of different techniques—absorption, one-step inhibition and counterstaining—for elimination of cross reactions. Acta Derm Venereol (Stockh) 1965; 45: 61–73.
8. Ljunghall K. Dermatitis herpetiformis. Immunological aspects with special reference to a gluten-free diet. Uppsala Universitet 1982: 17.
9. Population statistics. Örebro, Sweden: Central Statistics Bureau, 1983.
10. Leonard JN, Haffenden GP, Ring NP, McMinn RMH, Sidgwick A, Mowbray JF, Unsworth DJ, Holborow EJ, Blenkinsopp WK, Swain AF, Fry L. Linear IgA disease in adults: Br J Dermatol 1982; 107: 301–316.
11. Morris JN. Uses of epidemiology. 3rd ed. Edinburgh, London and New York: Churchill Livingstone 1975: 266.
12. Fry L, Seah PP, Riches DJ, Hoffbrand AK. Clearance of skin lesions in dermatitis herpetiformis after gluten withdrawal. Lancet 1973; i: 288–291.
13. Wyatt E, Shuster S, Marks JM. A postal survey of patients with dermatitis herpetiformis. Br J Dermatol 1971; 85: 511–518.
14. Burrows D. The prevalence of dermatitis herpetiformis. Br J Dermatol 1972; 88: 437.
15. Chorzelski TP, Jablonska S. Diagnostic significance of the immunofluorescent pattern in dermatitis herpetiformis. Int J Dermatol 1975; 14: 429–436.
16. Fry L, Haffenden G, Wojnarowska F, Thompson BR, Seah PP. IgA and C'3 complement in the uninvolved skin in dermatitis herpetiformis after gluten withdrawal. Br J Dermatol 1978; 99: 31–37.
17. Ljunghall K, Tjernlund U. Dermatitis herpetiformis: Effect of gluten-restricted and gluten-free

diet on dapsone requirement and on IgA and C'3 deposits in uninvolved skin. Acta Derm Venereol (Stockh) 1983; 63: 129–136.
18. Seah PP, Fry L. Immunoglobulins in the skin in dermatitis herpetiformis and their relevance in diagnosis. Br J Dermatol 1975; 92: 157.
19. Jablonska S, Chorzelski T, Beutner EH. Indications for skin and serum immunofluorescence in dermatology. In: Beutner EH, Chorzelski TP, Beam SF. eds Immunopathology of the skin. 2nd ed. New York, Chichester, Brisbane, Toronto: Wiley Medical Publication, J. Wiley & Sons, 1977: 21.
20. Mobacken H, Kastrup W, Ljunghall K, Löfberg H, Nilsson L-Å, Svensson Å, Tjernlund U. Linear IgA dermatosis: A study of ten adult patients. Acta Derm Venereol (Stockh) 1983; 63: 123–128.
21. Katz ST, Strober W. The pathogenesis of dermatitis herpetiformis. J Invest Dermatol 1978; 70: 63–75.
22. Frödin T, Gotthard R, Hed J, Norrby K, Walan A. Gluten-free diet for dermatitis herpetiformis: The long-term effect on cutaneous, immunological and jejunal manifestations. Acta Derm Venereol (Stockh) 1981; 61: 405–411.
23. Brow JR, Parker F, Weinstein WE, Rubin CE. The small intestinal mucosa in dermatitis herpetiformis. I. Severity and distribution of the small intestinal lesion and associated malabsorption. Gastroenterology 1971; 60: 355–361.
24. Fry L, Leonard JN, Swain F, Tucker WFG, Haffenden G, Ring N, McMinn RM. Long term follow-up of dermatitis herpetiformis with and without dietary gluten withdrawal. Br J Dermatol 1982; 107: 631–640.