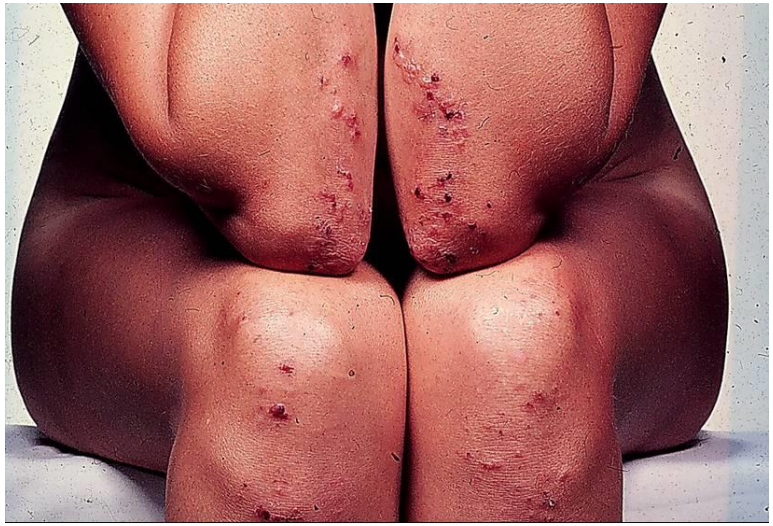
Dermatitis herpetiformis:
Skin manifestation of coeliac disease



Coeliac UK Research Conference 2018

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NO CONFLICTS OF INTEREST

History of Dermatitis Herpetiformis

1884
- ***Duhring L***
  - Clinical picture of DH described
  - ”Dermatitis Herpetiformis”

1969
- ***Van Der Meer JB***
  - Immunofluorescence finding typical for DH described

1966
- ***Marks J***
  - 70% of DH patients have enteropathy

1969
- ***Fry L***
  - Gluten-free diet is the treatment for DH rash

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Dermatitis herpetiformis

= is an extraintestinal manifestation of coeliac disease

- ***Similar enteropathy in both***
- ***Same etiological environmental factor currently identified*** (gluten in wheat, rye and barley)
- ***Similar genetic background as in coeliac disease***
  - Strong association with HLA DQ2/DQ8
  - Cluster in the same families and identical twins
- ***Autoantibody response against transglutaminase 2 in both***

= is a chronic, itching and blistering skin disorder

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Epidemiology of Dermatitis Herpetiformis

- Prevalence of DH has previously ranged from 10 to 39/100 000
- In Finland the prevalence of DH was 75/100 000 (1/1300) *(Salmi TT et al. Brit J Dermatol 2011;165:354-9)*
  - 1/8 coeliac disease patients have DH
- In UK the prevalence of DH was 1/3300 *(West J, et al. Am J Gastroenterol 2014;109:757-768)*
  - 1/8 coeliac disease patients have DH
- In Finland the incidence of DH was 3.5 per 100 000 (1970-2009)
- In UK the incidence of DH was 1.2 per 100 000 (1991-2011)

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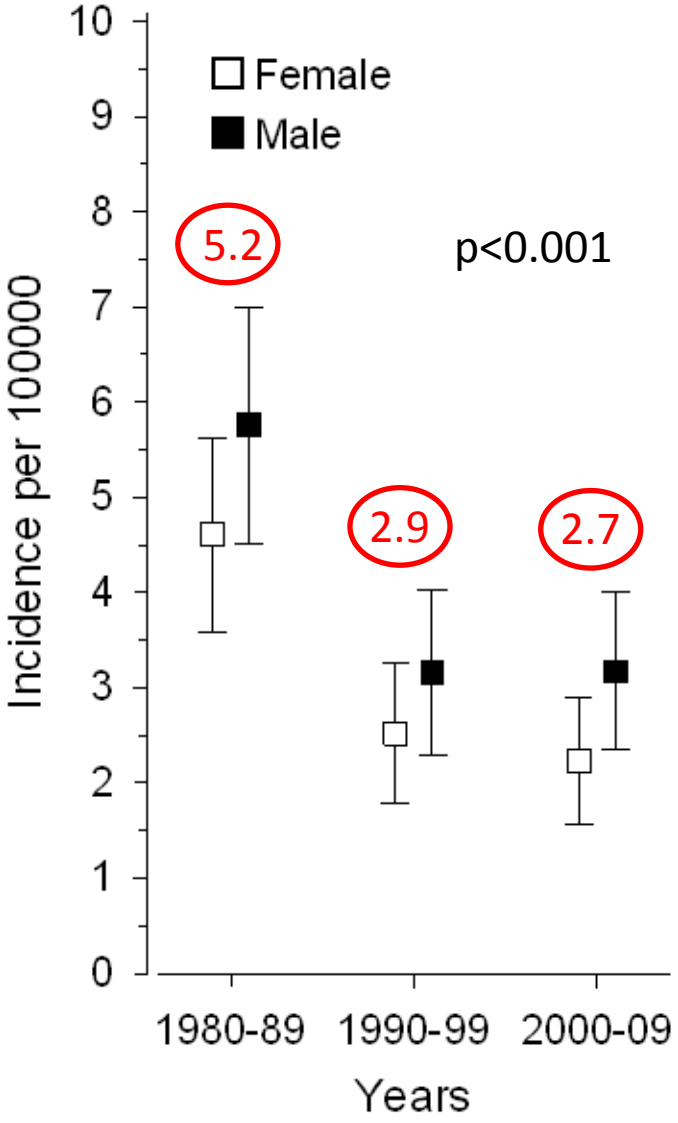
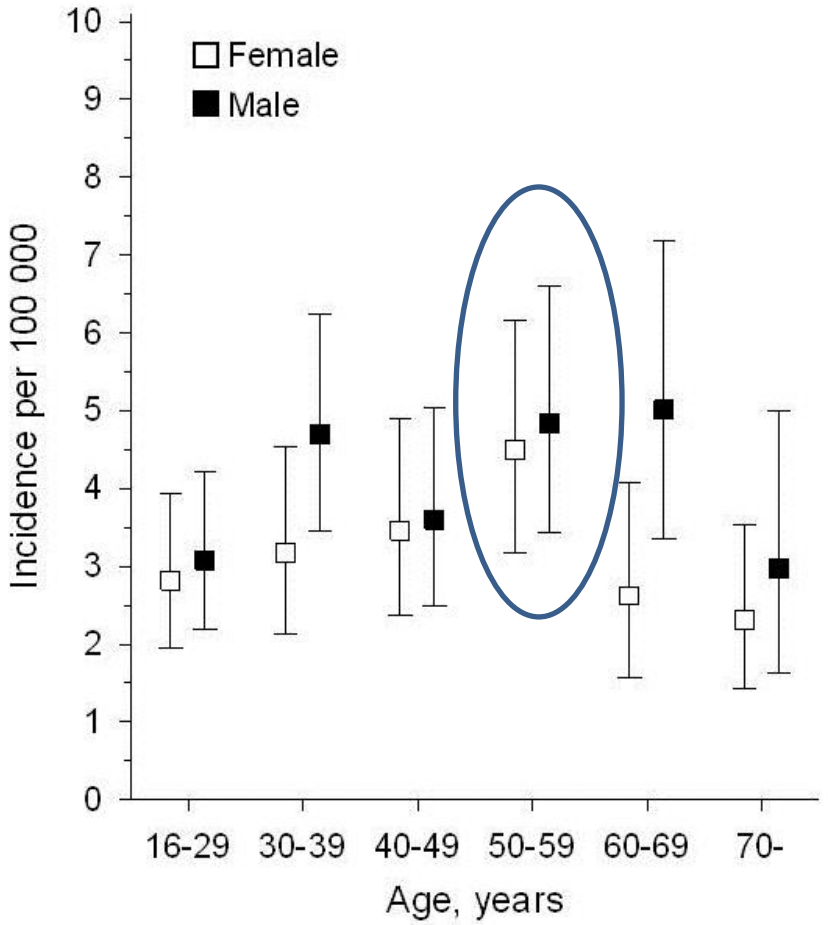
Incidence of Dermatitis Herpetiformis in Finland

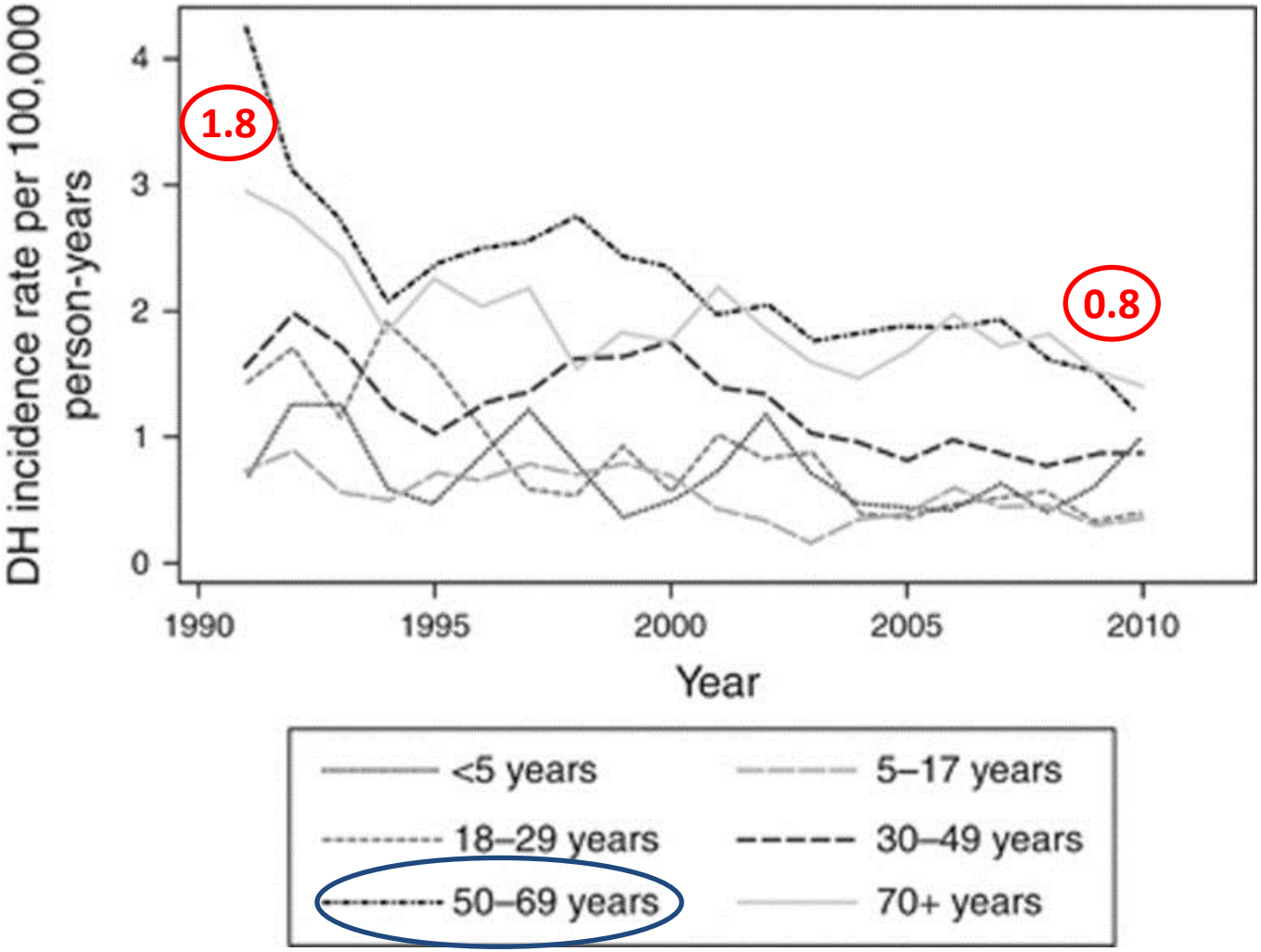
Salmi T et al. Br J Dermatol 2011;165:354-9.





Incidence of Dermatitis Herpetiformis in UK

West J, et al. Am J Gastroenterol 2014;109:757-768.



Epidemiology of Dermatitis Herpetiformis

- Incidence of DH almost identical in males and in females (In Finland and in UK)
- In UK 8% of DH patients were ≤ 17 years of age at the time of the diagnosis
- In Finland 4% patients were <16 years of age at the time of the diagnosis

Mean ages of the 477 patients with dermatitis herpetiformis at diagnosis in the whole series and in the 10-year periods of the study.

	All patients (n)	Males (n)	Females (n)
Whole series 1970-2009	42.8 ± 17.1* (477)	42.8 ± 16.4 (250)	42.8 ± 17.9 (227)
1970-1979	35.8 ± 14.6 (87)	35.3 ± 15.5 (44)	36.3 ± 13.8 (43)
1980-1989	40.7 ± 15.5 (177)	39.9 ± 15.1 (93)	41.6 ±16.0 (84)
1990-1999	46.1 ±16.3 (101)	44.7 ± 13.8 (53)	47.6 ± 18.7 (48)
2000-2009	48.6 ± 19.4 (112)	51.1 ± 17.5 (60)	45.8 ± 21.2 (52)

**Mean ± SD*

Salmi T et al. Br J Dermatol 2011;165:354-9.

Clinical presentation of DH

- Itching, blistering rash
- Typical sites elbows, knees and buttocks
  - Upper back, abdomen, groin, axillae, scalp and face can be affected, oral lesions are rare
- Presentation and activity varies between individuals and can fluctuate

→ Due to itching and scratching, blisters are often eroded and only crusts and excoriations are seen in typical DH rash locations

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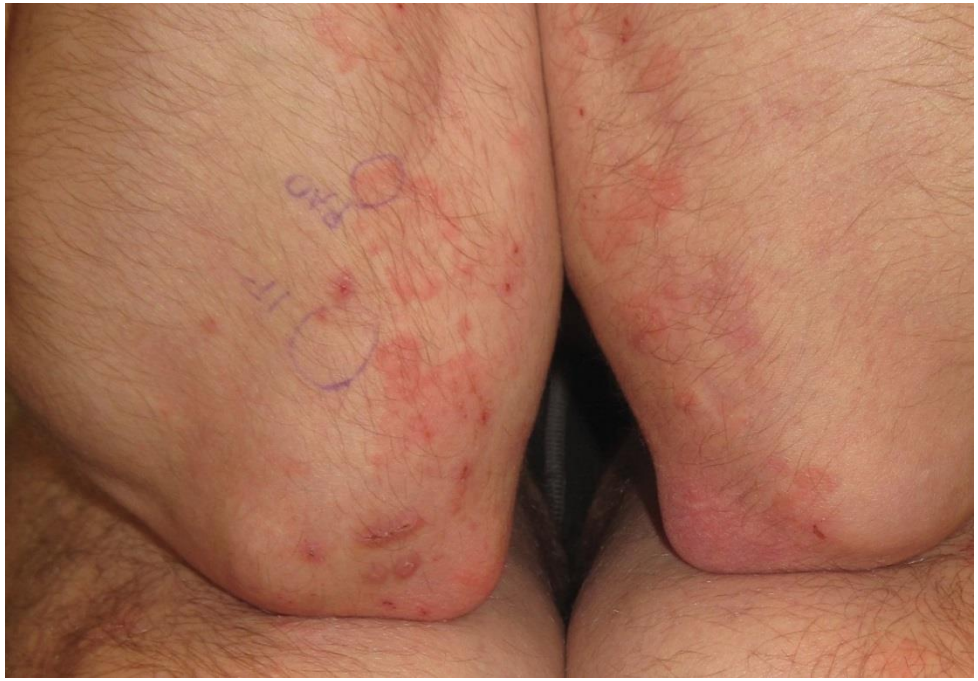
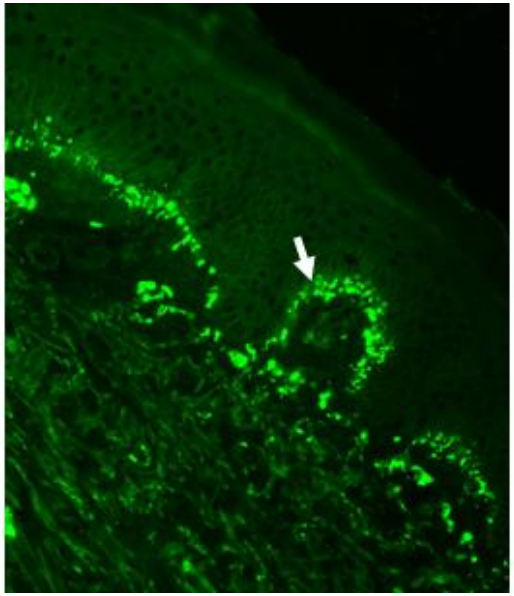
DH diagnosis

- Skin biopsy is taken from the perilesional skin and studied with direct immunofluorescence
  - Pathognomonic IgA deposits are detected in the papillary dermis



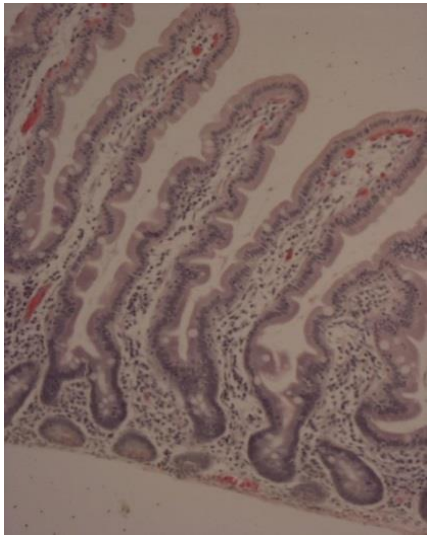


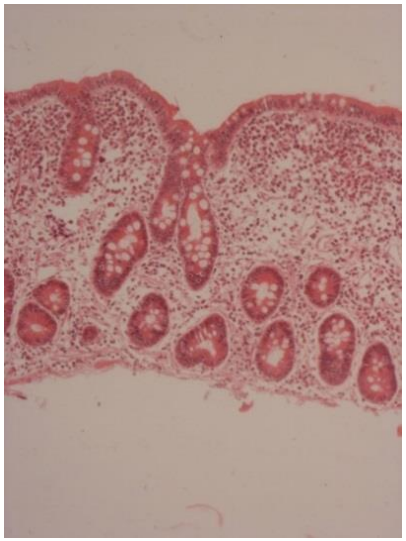
IgA is directed against epidermal Transglutaminase (TG3)

(Sárdy M et al. J Exp Med 2002;195:747-57)

Small bowel mucosa in DH

- Small bowel biopsies are not necessary for diagnostic purposes
- In Finland gastroscopy and small bowel biopsy are indicated at the time of the diagnosis for patients >40 years of age and those with abdominal symptoms or signs of malabsorption
- ¾ of DH patients have villous atrophy in the small bowel mucosa
- The remaining ¼ have coeliac type inflammation in the mucosa





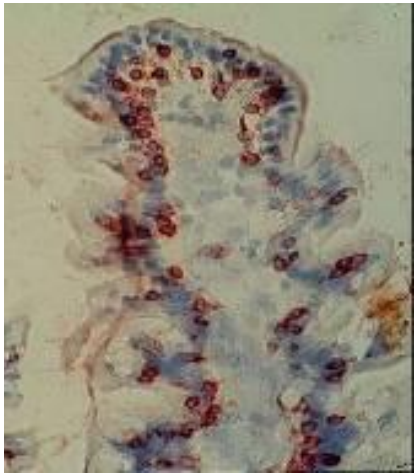
- Obvious gastrointestinal symptoms are rare (1/3 have minor symptoms)

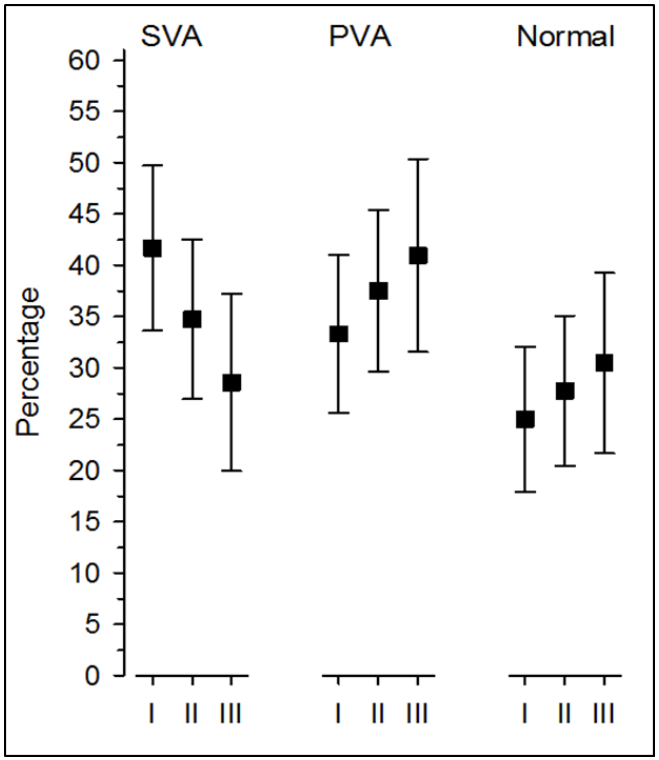
Small bowel mucosa in DH

- Density γδ T cells is typically increased

(Savilahti et al. Gut 1992;33:206-11,

Järvinen TT et al. Am J Gastroenterol 2003;98:1332-7)





393 DH patients with small bowel biopsy result

I = 1970-1984 (n=144)

II= 1985-1999 (n=144)

III= 2000-2014 (n=105)

The prevalence of SVA has decreased significantly (p=0.032)

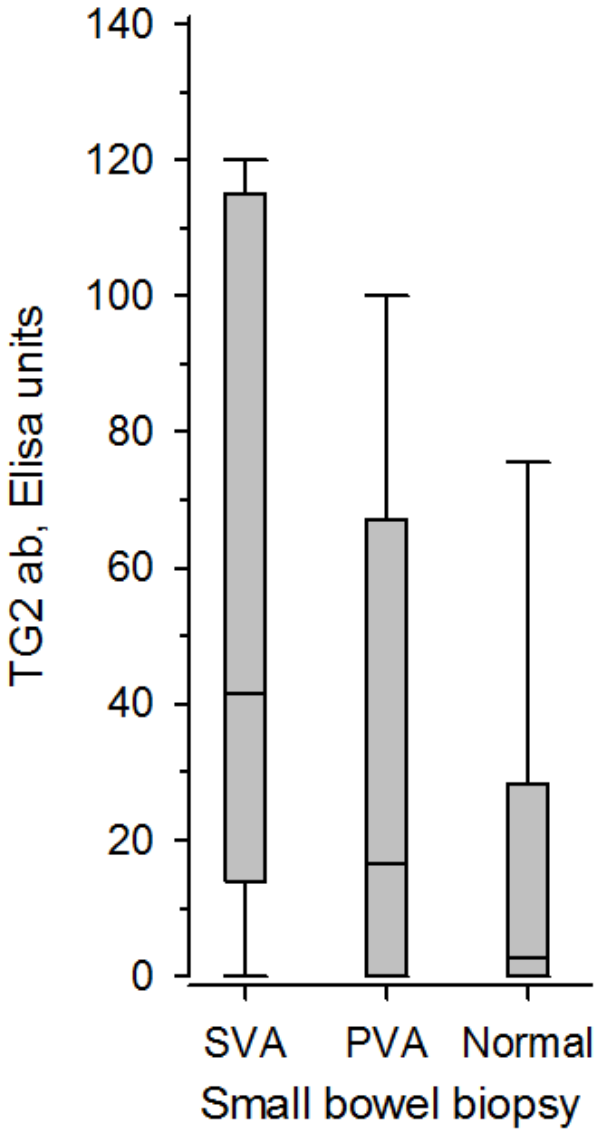
(Mansikka E, et al. J Clin Gastroenterol 2017;51:235-9)

The diagnostic delay of DH has decreased from 12 months to 8 months

(Mansikka E, et al. Acta Derm Venereol 2018;98:195-99)

The severity of DH rash has not changed since 1970

Coeliac autoantibodies in DH



autoantibodies to tissue
2) in the sera *(Dieterich et al. J Invest Dermatol*

antibodies are both TG2 targeted and
ce

oeliac autoantibodies is somewhat lower
eliac disease

tibody positivity in DH correlates with
owel mucosal damage

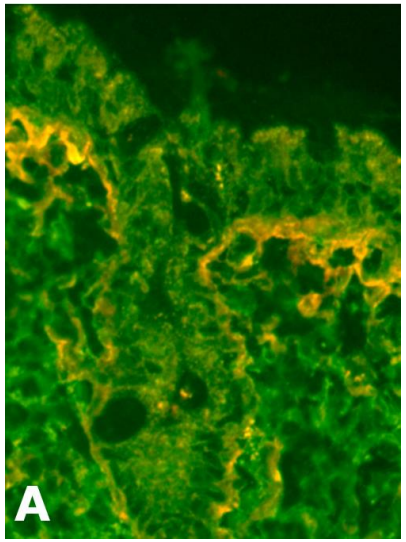
Patients with SVA and PVA have significantly higher TG2 antibody levels than the patients with normal mucosa

(Mansikka E, et al. J Clin Gastroenterol 2017;51:235-9)

Autoantibodies in DH

- In coeliac disease TG2 antibodies are produced in the small bowel mucosa
  - There are TG2 targeted IgA deposits in the gut

  (Korponay-Szabo et al. Gut 2004;53:641-8)
- 79% (37/47) of untreated DH patients evince TG2 specific IgA deposits in the small bowell mucosa *(Salmi TT et al. Acta Derm Venereol 2014;94:393-7)*
  - TG2 specific IgA deposits show association with the degree of villous atrophy and are gluten-dependent



- Circulating TG3 antibodies have also been detected in the serum of DH patients *(Sárdy M et al. J Exp Med 2002;195:747-57)*
  - Serum TG3 antibodies are gluten-dependent in DH
  - Some coeliac disease patients without DH also have serum TG3 antibodies
    - *Marker of subsequent DH development??*

Treatment of DH

- Gluten-free diet is the treatment of choice *(Fry L, et al. Arch Dermatol 1969;100:129-35)*
  - 98% of Finnish DH patients follow GFD
    - Strictness of the diet: 72% no faults, 19% faults once in a month, 8% faults several times a month. 85% of DH patients use oats *(Hervonen et al. Br J Dermatol 2012;167:1331-7)*
- Additional treatment with dapsone is indicated in patients with severe skin symptoms
  - 65% of Finnish DH patients start dapsone (initial daily dose 25-50mg)
  - Dapsone causes rapid relief of rash (within 2-3 days)
  - Dapsone is generally used for 1-2 years

Refractory DH?

- *Hervonen K et al. Acta Derm Venereol 2016;96:82-6*
- **Refractory DH** = GFD duration at least 3 years, dapsone treatment still needed (dose at least 75mg/week) to control the DH rash
- Prevalence of refractory DH was 1.7% (7/403)
  - Median duration of GFD 16 years
  - All refractory DH patients investigated had normal small bowel mucosal histology
  - 83% (5/6) of refractory DH patients had IgA deposits in the skin (compared to 19% in the control group)
  - No difference between gastrointestinal symptoms between refractory DH patients and controls

Refractory DH is rare and differs from refractory coeliac disease

- Normal small bowel mucosa, no development of lymphoma

Prognosis of DH

- DH patients have increased risk of concomitant autoimmune diseases and lymphoma similarly as coeliac disease patients
  - Adherence to GFD reduces the risk for lymphoma *(Hervonen K, et al. Brit J Dermatol 2005;152:82-6)*
- **Bone complications in DH**?
  - Only a few conducted studies on bone mineral density in DH and conflicting results (BMD normal or slightly lowered)
  - Fracture risk is not increased in DH *(Lewis et al. Aliment Pharmacol Ther 2008;27:1140-7)*
- **Mortality in DH**
  - Mortality in DH has shown to be decreased in a few conducted studies
  - In a Finnish study the all-cause mortality and mortality for deaths due to cerebrovascular diseases were lower among DH patients compared to the general population *(Hervonen et al. Br J Dermatol 2012;167:1331-7)*
    - DH patients reported significantly less hypercholesterolemia and there were fewer current and past smokers compared with the age- and sex-matched control population

Burden of DH

- Lowered quality of life (QoL) is associated with several chronic skin diseases and also untreated coeliac disease
- QoL in coeliac disease increases along with gluten-free diet treatment
- **Very little knowledge about QoL in DH**

- *Pasternack C, et al. Acta Derm Venereol 2017;97:58-62, Pasternack C, et al. Am J Clin Dermatol 2015;16:545-52)*
- QoL is lower in untreated DH compared to controls, and QoL is lower at diagnosis in those with gastrointestinal symptoms (38%) compared to those without
- After 1 year of GFD and in long-term treated DH patients QoL is comparable to that of controls

Long-term prognosis of DH patients on GFD is excellent

Thank you for your attention

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