CASE REPORT

Dermatitis herpetiformis in siblings

Chmurova N[1], Parnicka Z[2], Svecova D[1], Manova A[1], Simaljakova M[1]

Department of Dermatovenerology, Faculty of Medicine, Comenius University, Bratislava, Slovakia. **nada.chmuroav@centrum.sk**

Abstract

Two Caucasian sisters, XZ and YZ, suffered from DH. However, the clinical course of their diseases was different; patient XZ, contrary to her sister YZ, suffered besides dermatitis herpetiformis (DH) also from coeliac disease (CD) and an autoimmune thyroid disease. The sisters were ordered to adhere to gluten-free diet and dapsone was prescribed, however, patient XZ developed a hypersensitivity to dapsone. The HLA typing disclosed that they were homozygous and that they shared HLA alleles DQB1*0201. Our results confirm the known association of DH to other autoimmune disorders and its well established association the HLA-DQB1*0201 allele. Although DH is generally not regarded as a familial disease our case report suggests its familial character *(Fig. 3, Ref. 10)*. Full Text (Free, PDF) *www.bmj.sk*.
Key words: dermatitis herpetiformis, coeliac disease, HLA typing, siblings.

Dermatitis herpetiformis (DH) is an autoimmune, life-long, blistering, pruritic skin disease with pathognomic IgA deposits in the papillary dermis. It is characterized by grouped excoriations, erythematous, urticarial plaques and papules with vesicles that appear on the elbows, knees, back, and buttock. It is more common in men than women (ratio of 3:2) and the onset of the disease is usually in adolescence or young adulthood (1). Prevalence in Caucasian population has been reported as high as 10 cases per 100 000 (2). DH and coeliac disease (CD) are both gluten-sensitive diseases which share a common immunogenetic background (1, 3). Classical CD and DH can be regarded as two major outcomes of gluten sensitivity (4). Both diseases have a strong genetic association to HLA alleles, especially to HLA-DQA1*0501 and DQB1*0201, which encode the HLA-DQ2 heterodimer (2). CD is known to cluster in families, whereas there is only a little such evidence for DH. Besides gluten-free diet, sulfones, predominantly dapsone, are often used as a therapy. There is an association of DH to other autoimmune diseases, especially autoimmune thyroid disease (in 4.3 % of DH patients) followed by insulin dependent diabetes (DM1A), systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, and vitiligo or alopecia areata (3, 5).

Case report

Two Caucasian sisters, XZ and YZ, suffered from DH. However, the clinical course of their diseases was different.

A 38-years old Caucasian female patient (XZ) was admitted to hospital in September 2006 due to pruritic erythematous eruptions that had appeared about a half year ago. The lesions were localized symmetrically on the elbows, knees, dorsal parts of the hands, buttock and sacral area. Previously she had been treated with topical corticosteroids and oral antihistamines for the last four weeks, however without a major effect.

Her personal history revealed that she had suffered from CD for 2 years, which was manifested as diarrhea, dyspepsia, pyrosis and pain in the epigastric region. According to her own data, she has been suffering from intermittent abdominal difficulties since her childhood. Serological examinations revealed positive antigliadin antibodies (IgG +, IgA +++), antiendomysial antibodies (++++), and antireticulin antibodies (++++). Histopathological investigations of the duodenal mucosa disclosed an increased intraepithelial lymphocytosis with focal cryptal hyperplasia and branching and a focal partial to subtotal villous atrophy. So, both

[1]Department of Dermatovenerology, Faculty of Medicine, Comenius University, Bratislava, and [2]Department of Immunology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

Address for correspondence: N. Chmurova, MD, Dept of Dermatovenerology, Faculty of Medicine, Comenius University, Mickiewiczova 13, SK-813 69 Bratislava 1, Slovakia.
Phone: +421.2.57290480

Acknowledgement: The study was supported by the Research Programs of the Ministry of Education of the Slovak Republic VEGA 1/3437/06.

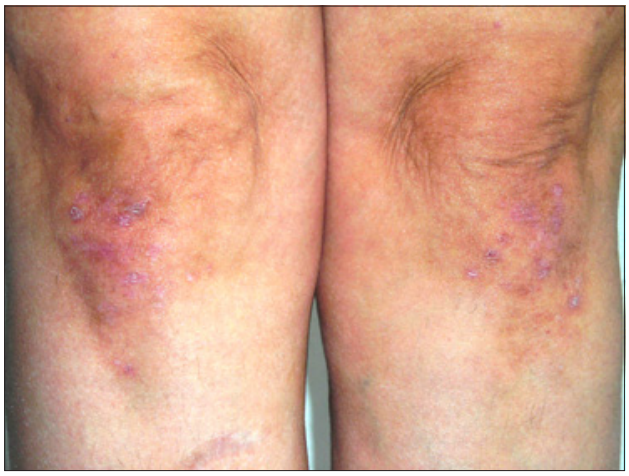

Fig. 1. Patient suffering from dermatitis herpetiformis. Erythematous papules and plaques with crusts and erosions on the knees (sister XZ).

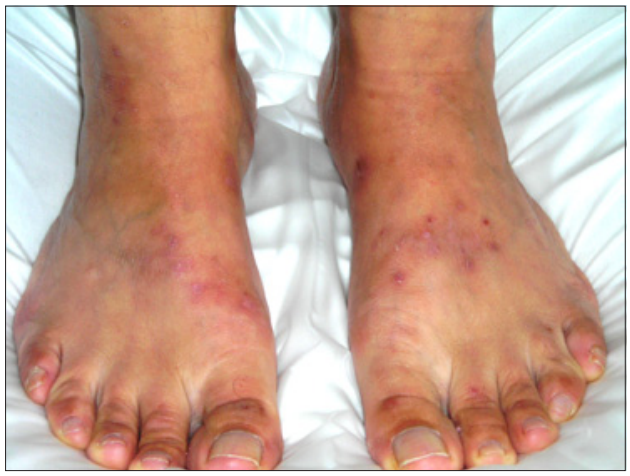

Fig. 2. Patient suffering from dermatitis herpetiformis. Erythematous papules and plaques with crusts and erosions on the dorsa of the feet (sister XZ).

serological and histopathological examinations confirmed the diagnosis of CD. Serological examinations proved positive IgG antibodies to cow milk proteins. She was recommended to adhere to gluten-free diet, however, she was not strictly compliant. Since 2005 she has been suffering from chronic autoimmune thyroiditis, with symptoms of hypothyroidism and has been treated by systemic levothyroxinum natricum of 50 ug per day.

Her family history revealed that her elder sister has also been suffering from DH, her diagnosis of DH was established in 2003.

On admission, the physical examination showed erythematous papules and plaques with crusts and erosions which were present in symmetrical pattern on the elbows, dorsa of the hands, knees, dorsa of the feet, buttock and sacral area (Figs 1 and 2).

Differential blood count and also hepatic and renal biochemical parameters showed normal values. Potassium iodine patch test was performed with a positive result. The lesion skin biopsy revealed a formation of subepidermal bullae and neutrophile accumulation in her epidermis. Thickened basement membrane, oedema at the papillary tips and neutrophile infiltration were found, too. Immunohistochemical examinations proved presence of IgA, traces of IgM and C3 in the involved tips of dermal papillae along the basement membrane zone. Both, histopathological and direct immunohistochemical examinations of the skin biopsy confirmed the diagnosis of DH.

Gluten-free diet was recommended, and dapsone 100 mg per day was administered. Dapsone had to be discontinued on day 10, because drug allergy was suspected as difficulties with breathing, swelling of the tongue, fever, cefalea, weakness and maculous rash developed. The allergy to dapsone was confirmed by in vitro lymphocyte transformation test. The value of methemoglobinaemia was 3.0 %. The response to gluten-free diet was good what resulted in refraining of DH-specific drugs. The autoimmune thyroiditis was controlled with the 50 μg of levothyroxinum natricum per day. She has not been consuming milk or dairy products. No recurrence of DH or CD appeared during her 11-months follow-up period.

The patient YZ (sister) is a 39 years old female, with a 4 year history of DH. She was admitted to hospital in September 2003 due to 2 months lasting eruption of pruritic papules and vesicles, followed by formation of erosions and crusts. They appeared mostly on elbows, dorsa of hands, knees and face. She was treated with antihistamines and topical therapeutics with no effect.

Physical examinations showed that intensely pruritic excoriated erythematous papules were distributed predominantly on the extensor surfaces of elbows and knees and also on the forehead and nose. No symptoms of gastrointestinal discomfort were present.

Histopathological and direct immunohistochemical examinations of a skin confirmed the diagnosis of DH with a deposition of IgA in granular pattern in the upper papillary dermis.

Laboratory examinations as differential blood count and hepatic and renal biochemical parameters were within normal limits.

Potassium iodine patch test (10 % concentration) was carried out with a positive result.

Serological examination for CD showed a negative result of the anti-gliadin/-reticulin antibody tests and proved remarkable presence of IgG antibodies to cow milk proteins. The value of methemoglobinaemia was 2.22 %.

The patient was ordered to adhere to gluten-free diet. Dapsone was prescribed (100 mg per day) and skin symptoms and pruritus were subsequently brought under the control. She could discontinue dapsone after 2 years on the diet. There was no recurrence of the DH lesions during 4 years of the follow-up period.

HLA typing

Blood samples were drawn into EDTA solutions and DNA was isolated by a salting out method (6). HLA-DQB1 genotyping was performed at low resolution level (Fig. 3) followed by a high resolution typing of DQB1*02 gene. A polymerase chain reaction-using the sequence specific primers (PCR-SSP) was used (7). Primer mixes were manufactured by Olerup, SSP AB, Sweden.

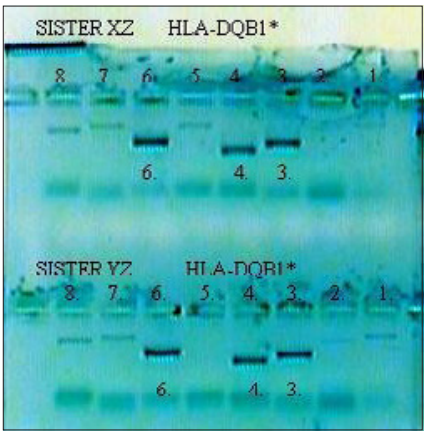

Fig. 3. HLA-DQB1* genotyping of siblings suffering from dermatitis herpetiformis. HLA typing-sisters XZ and YZ share HLA-DQB1* alleles. Missing specific product with primer mix numer 1, 2, 5, 7, and 8 means, that the patient does not possess alleles DQB1*030101-*0628. Positive band in reactions 3, 4, 6 means, that the patient has one or two of serological DQ2 alleles (DQB1*0201-*0204).

The low resolution genotyping disclosed that both sisters shared HLA-DQB1* allele. The subsequent high resolution typing identified the allele being DQB1*0201. As no other specific product was found, it could be concluded that they were homozygous, i.e. HLA-DQB1*0201/ DQB1*0201. HLA-DQB1*0201 allele codes the HLA-DQ2 molecules identified by serologic techniques.

Discussion

Two sisters suffering from DH were studied. The patient "XZ" began with CD, followed by DH symptoms two years later. Her sister "YZ" never developed CD, she suffered only from DH. Later, when she was on gluten-free diet for a period of 4 years, she was serologically examined for CD, with negative results. The negative CD serological examinations could be, however, influenced by gluten-free diet. Patient "XZ" also suffered from an autoimmune thyroid disease.

DH is generally regarded as a disease with no familiar bias. Some authors, e.g., Reunala (1996), however claim that DH is a familiar disease with about 10 % patients having one or several first-degree relatives affected by DH or CD. The diseases in their relatives were either DH (4.4 %) or CD (6.1 %) (8). Hervonen et al (2002) found in the long-term follow-up study of CD and DH, that in every fifth patient the first-degree relatives were affected, and that the prevalence among relatives was 5.5 %. The incidence of either DH or CD in relatives is from 10 to 15 times higher than expected (9). DH segregates also in families of patients with CD, and vice versa, indicating the same genetic background. CD and DH were mixed in several multiple-case families (9). However, even genetically identical individuals, as proved in the study of six monozygous twin pairs, can have clearly different phenotypes, either DH or CD. These results suggest that environmental factors determine the exact phenotype of this multifactorial disease (10).

Both DH and CD are known to be associated with HLA alleles. About 90% of DH patients carry HLA-DQ2 (i.e. determined by alleles DQA1*0501 and DQB1*02) either in cis-position with DRB1*03 or in trans-position with DRB1*05/07. The remaining patients usually express the HLA-DR4-DQ8 haplotype, with few exceptions (4). Our results confirm the association with DQB1*02. The high resolution HLA typing revealed that both sisters were HLA-DQB1*0201 in homozygous configuration, resulting in HLA-DQ2/DQ2 phenotype. A similar situation was found in the study of six monozygous twins where 5 of 6 twin pairs were homozygous for one or more predisposing alleles (10). Homozygous form of an HLA allele is rarely observed in healthy controls, less than statistical incidence, what indicates that the double genetic load favours the development of the disorder.

Conclusion

The sisters XZ and YZ were found to have the same genetic background and typical risk alleles HLA-DQB1*02. Even though they were HLA- DQ2 homozygous with a high probability, they showed a different course of the disease. Despite the fact that dermatitis herpetiformis is not generally regarded as a familial disease, this case report points to its familial character.

References

1. Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC (Eds). Dermatology. Berlin; Springer, 2000: 1853

2. Reunala T. Dermatitis herpetiformis: coeliac disease of the skin. Ann Med 1998; 30 (5): 416—418.

3. Buc M. Autoimunita a autoimunitné choroby. Bratislava; VEDA 2005: 493 pp.

4. Karell K, Korponay-Szabo I, Szalai Z, Holopainen P, Mustalahti K, Collin P, Maki M et al. Genetic dissection between coeliac disease and dermatitis herpetiformis in sib pairs. Ann Hum Genet 2002; 66: 387—392.

5. Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Brit J Dermatol 1997; 136: 315—318.

6. Miller S, Dykes D, Polesky H. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acid Res 1988; 16: 1215.

7. Fazekašová H, Shawkatová I, Buc M, Ferenčík S. HLA-DRB1* and -DQB1* allele frequencies in Slovak population. Bratisl Lek Listy 1998; 99: 601—604.

8. Reunala T. Incidence of familial dermatitis herpetiformis. Brit J Dermatol 1996; 134 (3): 394—398.

9. Hervonen K, Hakanen M, Kaukinen K, Collin P, Reunala T. First-degree relatives are frequently affected in coeliac disease and dermatitis herpetiformis. Scand J Gastroenterol 2002; 37 (1): 51—55.

10. Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, Reunala T. Concordance of Dermatitis Herpetiformis and Celiac Disease in Monozygous Twins. J Invest Dermatol 2000; 115: 990—993.

Received September 10, 2007.
Accepted October 20, 2007.