

CLINICAL REPORT

Dermatitis Herpetiformis Presenting as Ataxia in a Child

Per HELSING¹ and Hege FRØEN²

Departments of ¹Dermatology and ²Rheumatology, Rikshospitalet University Hospital, Oslo, Norway

Dermatitis herpetiformis and coeliac disease are gluten-sensitive diseases that share immunopathological mechanisms. Neurological disorders are reported in both diseases, being more frequent in coeliac disease. Dermatitis herpetiformis is rare in paediatric populations and only sporadic cases with neurological dysfunction are reported. Uncertainty exists as to whether early treatment may stop or reverse neurological symptoms. We describe here the case of a child presenting with a rash and ataxia, diagnosed with dermatitis herpetiformis, in whom neurological symptoms and signs regressed after treatment. Key words: ataxia; coeliac disease; child; chronic bullous disease of childhood; dermatitis herpetiformis.

(Accepted November 8, 2006.)

Acta Derm Venereol 2007; 87: 163–165.

Per Helsing, Department of Dermatology, National Hospital, NO-0027 Oslo, Norway. E-mail: per.helsing@rikshospitalet.no

Gluten sensitivity may present as coeliac disease (CD) or dermatitis herpetiformis (DH). These conditions are believed to share immunopathological mechanisms and have the same genetic background, being linked to the human leukocyte antigen (HLA) class II genes coding for DQ2 molecules found in 98% of patients in Northern Europe (1, 2). Tissue transglutaminase (TGase) is considered the major auto-antigen in CD, while epidermal transglutaminase probably is more important in DH (3).

Both conditions are associated with neurological disorders, CD having the greatest potential for neurological complications. The most frequent conditions are reported to be polyneuropathy and spino-cerebellar ataxia. Other disorders are lower motor neurone disease, myelopathy, epilepsy and encephalopathy (4). The mechanism for associated neurological dysfunctions is considered to be vitamin deficiency, toxic or metabolic alterations, or an immune-mediated process. Recent findings suggest that the ataxia in gluten-sensitive disorders is immune mediated (5). Uncertainty exists as to whether neurological dysfunction is reversible after treatment.

We report here a child with DH and neurological dysfunction that reversed on treatment.

CASE REPORT

The patient was a previously healthy boy, 2.5 years of age at presentation. He had no atopic disposition, no history of asthma or suspected allergy. At the age of 2 years he was diagnosed with atopic eczema presenting with an itchy rash, but worsening on treatment with topical steroids. He developed blisters, treated with cephalosporin under suspicion of impetigo contagiosa. His parents noted weakness in his arms and legs, and he exhibited a clumsy gait. He was transferred to our hospital on suspicion of a rheumatic condition.

At presentation, he complained of pain in the arms and legs, and intense itching of the skin. He was using a wheelchair and had difficulty standing without support (Fig. 1). His rash was symmetrical and generalized, consisting of erythematous papules, papulovesicles and scratch marks (Fig. 2). There was marked distal muscular atrophy, especially apparent in the thenar muscles (Fig. 3). He experienced pain in his legs, but had no gastrointestinal symptoms.



Fig. 1. Ataxia, in need of support in the upright position.



Fig. 2. Symmetrical, widespread, papulovesicular rash.

The findings of muscular atrophy, peripheral paresis and reduced tendon reflexes were subsequently confirmed under clinical examination by the paediatric neurologists. Based on the results of clinical examination, muscular biopsy, neurography, cerebral magnetic resonance imaging (MRI) and cerebrospinal liquid examination, paediatric neurologists arrived at a diagnosis of peripheral neuropathy.

The patient's haematological profile was normal. Folate in red blood cells was reduced to 250 nmol/l (range 315–835 nmol/l). Vitamin B12, D and E showed normal values. He was HLA-DQ2 positive and TGase antibodies (Varelista, Pharmasia Diagnostics, Uppsala, Sweden) were positive.

Neurography of nervus peroneus, suralis and medianus sinister demonstrated slow velocities and low motor and sensory action potentials. Muscular biopsy showed signs of denervation, compatible with polyneuropathy. Cerebral MRI and examination of cerebrospinal fluid were normal. A skin biopsy was unspecific, but direct immunofluorescence showed linear deposits of IgA in the basement membrane zone in normal and diseased skin. Indirect immunofluorescence was not performed, other auto-antibodies were normal. Duodenal biopsy performed at hospitalization was normal and the intra-epithelial lymphocyte count was not elevated. The duodenal biopsy was not repeated.

His condition was judged to be DH, and treatment was initiated with dapsone, 25 mg daily. He was put on a gluten-free diet with the addition of folate. The rash and itch disappeared after a few days, and after a few



Fig. 3. Distal muscular atrophy apparent in the thenar area.

months the muscular atrophy was no longer observed. His pinching ability returned to normal, and he was able to move without difficulty or support. At follow-up, the anti-TGase had returned to normal on a gluten-free diet. Two years later, he is still on treatment with dapsone, 25 twice daily, having experienced exacerbations of his skin condition at a reduced dosage.

DISCUSSION

We diagnosed this boy with DH based on morphology, a positive HLA-DQ2, positive TGase test and a well-known association between gluten-sensitive disease and neurological dysfunction. Immunofluorescence microscopy studies showed linear deposits of IgA in the basement membrane zone, suggesting chronic bullous dermatosis of childhood (CBDC). This entity is associated with the HLA groups HLA-B8, -CW7 and -DR3 and not with neurological dysfunction, but may respond to treatment with dapsone. The finding of linear deposits of IgA does not contradict DH, as it has been reported in subgroups of DH patients (6). It is possible that this patient had CBDC with coincidental CD, as described by Høgberg et al. (7). Repeated duodenal biopsies could have clarified this; however, he had no gastrointestinal symptoms, no indication of malabsorption and the exanthema was not typical of CBDC. The decision was made not to repeat the duodenal biopsy.

Nervous system involvement is reported in 10% of patients with CD, including neuropathy, ataxia, encephalopathy, seizures and psychiatric disturbances, in some instances with minimal or no enteric symptoms (8, 9). One case of CD associated with peripheral neuropathy in a child is reported in the literature. This child did not respond to treatment (10). The frequency of neurological dysfunction in DH is not known, but is probably much lower. One study of 305 patients with DH found no associated neurological disease (11), and neither did a small pilot study of 35 patients that looked specifically for neurological disease (9). DH is relati-

vely rare in children; one survey of 220 consecutive children with CD from a paediatric clinic found only one with DH (7).

Both peripheral and central nervous systems may be affected in gluten-sensitive diseases such as CD and DH. This supports the notion that gluten sensitivity is a systemic disease, capable of affecting multiple organs. IgA autoantibodies have been demonstrated in extra-intestinal tissue (liver, muscle and lymph nodes) in patients with CD (12), and a recent report found widespread IgA deposition around vessels in the brain of a patient with gluten ataxia, possibly disrupting the blood-brain barrier, allowing exposure of the CNS to gluten-related antibodies (5). We believe that an immune-mediated process is the most likely cause of polyneuropathy resulting in ataxia in this child. The reversal of neurological symptoms and signs and a normalization of anti-TGase on dapsone treatment suggest the same. No vitamin deficiency was found that could explain his neurological dysfunction.

This is the first report of a child with DH and neurological disease. Both his skin condition and neurological symptoms and signs reversed on treatment.

ACKNOWLEDGEMENT

We thank Mitch Loeb for assistance with the manuscript.

REFERENCES

1. Sollid L, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E. Evidence for primary association of celiac disease to a

- particular HLA-DQ alpha/beta heterodimer. *J Exp Med* 1989; 169: 345–350.
2. Sollid L. Molecular basis of celiac disease. *Annu Rev Immunol* 2000; 18: 53–81.
3. Sardy M, Karpati S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. *J Exp Med* 2002; 195: 747–757.
4. Hagen EM, Gjerde IO, Vedeler C, Hovdenak N. Neurological disorders associated with coeliac disease. *Tidsskr Nor Lægeforen* 2000; 120: 439–442.
5. Hadjivassiliou M, Mäki M, Sanders DS, Williamson CA, Grünewald RA, Woodroffe NM, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. *Neurology* 2006; 66: 373–377.
6. Seah PP, Fry L. Immunoglobulins in the skin in dermatitis herpetiformis and their relevance in diagnosis. *Br J Dermatol* 1975; 92: 157–166.
7. Høgborg L, Sokolski J, Stenhammar L. Chronic bullous dermatosis of childhood associated with celiac disease in a 6-year old boy. *Acta Derm Venereol* 2004; 84: 158–159.
8. Muller AF, Donnelly MT, Smith CML, Grundman MJ, Holmes GKT, Toghiani P. Neurological complications of coeliac disease: a rare but continuing problem. *Am J Gastroenterol* 1996; 91: 1430–1435.
9. Wills AJ, Turner B, Lock RJ, Johnston SL, Unsworth DJ, Fry L. Dermatitis herpetiformis and neurological dysfunction. *J Neurol Neurosurg Psychiatry* 2002; 72: 259–261.
10. Simonati A, Battistella PA, Guariso G, Clementi M, Rizzuto N. Coeliac disease associated with peripheral neuropathy in a child: a case report. *Neuropediatrics* 1998; 29: 155–158.
11. Reunala T, Collin P, Lewis HM, Fry L. Associated diseases and malignancy in dermatitis herpetiformis. In: Maki M, Collin P, Visakapi JK, editors. *Coeliac disease*. Tampere: Coeliac disease Study Group, 1997: p. 251–264.
12. Korponay-Szabo IR, Halttunen T, Szalai Z, Laurila K, Kiraly R, Kovacs JB, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. *Gut* 2004; 53: 641–648.