Eur J Pediatr (1989) 149:168–169

European Journal of
Pediatrics
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IgG_2/IgG_4 subclass deficiency in a patient with chronic mucocutaneous candidiasis and bronchiectases

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Abstract. A 22-year-old man with chronic mucocutaneous candidiasis (CMC) and hypothyroidism developed severe bronchiectases following recurrent bronchopneumonia. Immunological investigations revealed IgG_2/IgG_4 subclass deficiency and absence of antibodies against pneumococcal and Haemophilus polysaccharides. Under regular immunoglobulin substitution every 3 weeks pulmonary symptoms improved markedly.

Key words: IgG_2/IgG_4 subclass deficiency – Chronic mucocutaneous candidiasis – Bronchiectases

Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare disease characterized by persistent *Candida albicans* (CA) infection of the skin, nails and mucous membranes, usually beginning in the first months and persisting throughout life. There is frequent association with polyendocrinopathy, particularly hypothyroidism, hypoparathyroidism and Addison disease. In most patients a selective defect of cell mediated immunity against CA can be demonstrated [6]. The response of peripheral blood lymphocytes to other antigenic stimuli as well as humoral immunity reactions is mostly intact [3].

We report a patient with immunological features of CMC, but with additional deficiency of the IgG_2 and IgG_4 subclasses and inability to synthesize antibodies against pneumococcal and Haemophilus polysaccharides. Following recurrent bronchopneumonia the patient developed severe bronchiectases.

Case report

The 22-year-old patient had a non-contributory family history. Since the age of 3 months he had persistent CA infection of skin, nails and mucous membranes. Serum antibodies against CA were high. Delayed type skin reaction using candidine was negative. Cellular immunity was normal except for absent candidine stimulation of lymphocytes, as measured by radioactive thymidine incorporation. Since the age of 2 years he suffered from recurrent bacterial infections: pneumonia (7 times), acute bronchitis (5 times), sinusitis (4 times), otitis media (4 times), skin abscesses (4 times), panaritium (twice). In sputum and nasal swabs Pneumococcus and *Haemophilus influenzae* type B (HIB) could be repeatedly cultivated. At the age of 14 years he developed hypothyroidism without signs of polyendocrinopathy (no hypoparathyroidism, Addison disease or diabetes mellitus). Antithyroid antibodies were negative. At this time, long-term therapy with ketoconazole was started, which completely cleared the CA infection. After recurrent bacterial bronchitis and pneumonia, bronchiectases were diagnosed at the age of 15 years. Scintigraphy and lung function study revealed severe restrictive pulmonary disease.

When the patient was 20 years old, IgG subclass determination became available. Severe IgG_2 and IgG_4 deficiency was found (Table 1). The levels of total IgG, IgA and IgM, however, were normal, as were isoagglutinins and anti-tetanus IgG. The complement system (CH 50, AP 50, C 3, C 4) was normal, but very low levels of antibodies versus polysaccharides of Pneumococcus and HIB were found. Substitution therapy with intravenous immunoglobulins (0.4 g/kg every 3 weeks) was started, and no further progression of the respiratory tract dis-

Table 1. Humoral immunity in a patient with CMC

		Patient	Normal values
Serum immunoglobulins (g/l)			
IgG		12.9 / 17.58[a]	7.3 – 12.3
IgA		2.41/ 1.83[a]	1.09 – 2.74
IgM		1.95/ 1.03[a]	0.58 – 1.82
IgG_1		10.51/ 14.08[a]	7.55 ± 2.45
IgG_2		<0.09/<0.11[a]	3.8 ± 1.5
IgG_3		1.55/ 1.74[a]	0.73 ± 0.28
IgG_4		0.04/<0.07[a]	0.55 ± 0.63
Serum antibodies (titre × 10^{-1})			
IgG_1	PPS2	0	200
	PPS6	0	0
	PPS19	0	200
	PRP	0	100
IgG_2	PPS3	0	1600
	PPS6	0	800
	PPS19	0	800
	PRP	0	200

[a] Two determinations 4 months apart

PPS = pneumococcal polysaccharide; PRP = polyribosyl-ribitol-phosphatide

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Abbreviations: CA = *Candida albicans*; CMC = chronic mucocutaneous candidiasis; HIB = *Haemophilus influenzae* type B

ease was seen (stable scintigraphic and lung function studies over more than 1 year).

Methods

IgG, IgA and IgM levels were measured by nephelometry. IgG subclass concentrations were determined by radial immunodiffusion. Normal age matched values of IgG, IgA and IgM are expressed as percentiles (p10–p90) and of IgG_{1-4} as mean ±1SD [4, 5]. We determined normal values of serum antibodies in a serum pool of 50 normal adults vaccinated with pneumococcal polysaccharide and polyribosyl-ribitol-phosphatide, the capsular polysaccharide of HIB. The polysaccharide antibody levels were determined by the line-immuno-binding assay [1].

Discussion

The main immunological abnormalities found in CMC are selective skin anergy and in vitro lack of lymphocyte response towards CA. This is in keeping with a stimulusspecific defect in the production of certain lymphokines such as macrophage inhibition factor, i.e. an insufficient cellular immune response [2, 3]. In contrast, humoral immune reactions are usually intact. However, CMC patients with additional recurrent bacterial infections should always be carefully investigated for other concomitant immunological defects; a new possibility is Ig subclass deficiency. If an IgG_2/IgG_4 defect is detected, the levels of specific anti-polysaccharide antibodies (e.g. of pneumococcal antibodies before and after specific immunization) should be examined. Our patient with IgG_2/IgG_4 deficiency was unable to synthesize polysaccharide antibodies despite of repeated exposure to Pneumococcus and HIB.

If an IgG subclass deficiency leading to antibody deficiency is found, substitution therapy with immunoglobulins should be started to avoid severe pulmonary destruction. The simultaneous occurrence of CMC and IgG subclass deficiency has hitherto not been observed. This is partly due to technical reasons – routine measurement of IgG subclasses became available only a few years ago –, but on the other hand a systematic search for this humoral deficiency was not done. It should therefore be compulsory to measure IgG subclass concentrations in each case of CMC. For the moment, we can only speculate whether this combination has a common denominator, e.g. in the antigen-presenting cells being unable to process and present polysaccharide antigens, such as mannan from Candida and polyribosyl-ribitol-phosphatide from HIB, or whether this is a unique random coincidence.

References

1. Aeppli RE, Bargetzi MD, Binz H (1989) Diagnostic screening of multiple antigen-antibody-reactions in a new single assay on nitrocellulose: the line-immunobinding-assay (LIBA). J Immunol Methods 120:93–98
2. Durandy A, Fischer A, LeDeist F (1987) Mannan-specific and mannan-induced T-cell suppressive activity in patients with chronic mucocutaneous candidiasis. J Clin Immunol 7:400–409
3. Lehner T, Wilton JMA, Ivanyi L (1972) Immunodeficiencies in chronic muco-cutaneous candidiasis. Immunology 22:775–787
4. Morell A, Skvaril F, Hitzig WH (1972) IgG subclasses: development of the serum concentrations in "normal" infants and children. J Pediatr 80:960–964
5. Oxelius VA (1979) IgG subclass levels in infancy and childhood. Acta Paediatr Scand 68:23–27
6. Valdimarsson H, Higgs JM, Wells RS, Yamamura M, Horbes JR, Holt PJL (1973) Immune abnormalities associated with chronic mucocutaneous candidiasis. Cell Immunol 6:348–361

Received May 17, 1989 / Accepted June 6, 1989