LETTER TO JMG

Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis

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Chronic mucocutaneous candidiasis (CMC) includes a group of rare disorders with altered immune responses, selective against Candida, characterised by persistent and/or recurrent infections of the skin, nails, and mucous membranes, caused by organisms of the genus Candida, mainly *Candida albicans*. Familial occurrence of CMC was originally reported by Wells *et al*,[1] who described both males and females affected and consanguinity in a number of their pedigrees. The classification of CMCs is based on clinical features and pattern of inheritance, which can be either autosomal dominant or recessive (table 1). Most CMC types have an early age of onset, affect skin, nails, and mucous membranes, and are associated with altered phagocytosis and chemotaxis. The classical form of CMC does not include endocrinological diseases, which represent a major component of the immune polyendocrinopathy syndrome (APECED, MIM *240300), caused by mutations of the autoimmune regulator gene (*AIRE*) on chromosome 21q22.3.[2 3]

We describe a distinct form of familial chronic candidiasis (FCNC), characterised by early onset infections caused by different species of Candida, restricted to the nails of the hands and feet, associated with low serum concentration of intercellular adhesion molecule I (ICAM-1).

PATIENTS AND METHODS

The family originates from a rural village in Sicily and includes 11 affected subjects in five generations (fig 1). Based on clinical and anamnestic records, III.8 was the first affected member of this family. She developed nail dystrophy, presenting with hyperkeratosis and dark and thick nails, similar to those found in other family members. IV.5, a 71 year old female, was unaffected. V.4, a 48 year old female, was a blood relative of her husband. From the age of 6 months, she was affected by onycomycosis caused by Candida involving all the nails of her hands and feet (figs 2 and 3). Caustication was followed by regeneration of the nails, manifesting similar dystrophic features and Candida infection. V.7, a 47 year old male, was affected from birth by candidiasis of the nails of hands and feet, similar to her sister, V.4 (figs 2 and 3). She was the mother of three unaffected boys. V.10 and V.14, two females aged 37 and 33 years, related to V.4 and V.7, were also affected by chronic infections of all the nails of the hands and feet with onset in early infancy (figs 2 and 3). VI.3, a 20 year old man, was the son of first cousin parents (V.1 and V.2). The first symptoms of generalised onycomycosis occurred at the age of 3 months. VI.5, the 31 year old daughter of related parents (V.3 and V.4) manifested chronic candidiasis restricted to the nails of the feet from the age of 4 months (figs 2 and 3). Her 5 year old child was unaffected. VI.7, the 27 year old daughter of related parents (V.3 and V.4), had nail lesions similar to those of her sister VI.5 (figs 2 and 3). She was the

Key points

- Chronic mucocutaneous candidiasis (CMC) includes a group of rare genetic disorders with altered immune responses selective against Candida.
- We report an apparently distinct hereditary form of this disease, characterised by chronic infections caused by different species of Candida, occurring in 11 members in five generations of a family originating from a small village in Sicily.
- Notable features include neonatal onset with manifestations restricted to the nails of the hands and feet, associated with low serum concentrations of intercellular adhesion molecule I (ICAM-1).

Abbreviations: CMC, chronic mucocutaneous candidiasis; ICAM-1, intercellular adhesion molecule I; FCNC, familial chronic nail candidiasis; CSH, cell surface hydrophobicity; LFA-1, leucocyte function associated antigen-1

*The first two authors contributed equally to this work.

Table 1 Classification of CMCs

CMC type	Inheritance/MIM*	Onset
Familial chronic mucocutaneous candidiasis (FCMC) without endocrinopathy	Autosomal recessive 212050* Autosomal dominant 114580*	Childhood
With hypothyroidism	Autosomal dominant	Childhood
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)	Autosomal recessive 240300*	Childhood
Chronic localised candidiasis	Unknown	Childhood
Candidiasis with the hyper-IgE syndrome (Job syndrome)	Autosomal recessive 243700*	Childhood
Chronic mucocutaneous candidiasis with thymoma	Unknown	Adulthood
Candidiasis with chronic keratitis	Unknown	Childhood
Chronic oral candidiasis	Unknown	Adulthood

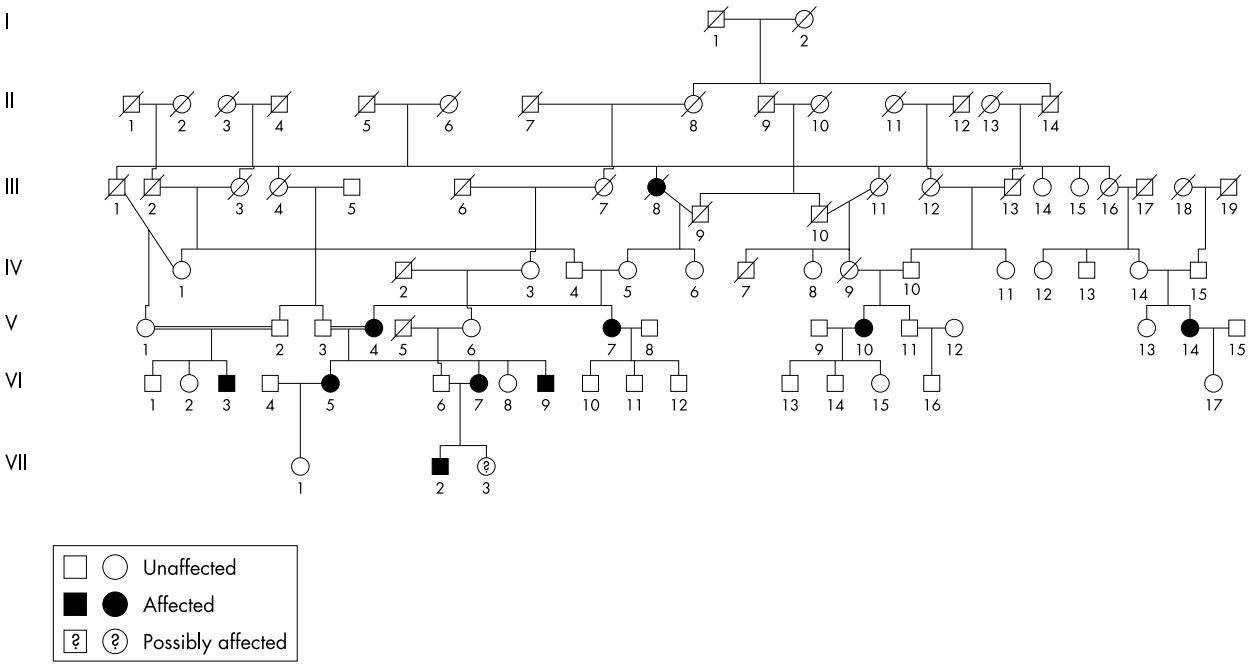

Figure 1 Pedigree of the family.

mother of a 5 year old child (VII.2), who showed candidiasis of the nails of the hands and feet from the age of 6 months (figs 2 and 3). Her 3 month old baby was unaffected. VI.9, the 14 year old son of related parents (V.3 and V.4), showed lesions in the upper and lower limb nails, similar to those of his sisters VI.5 and VI.7 (figs 2 and 3). All patients had

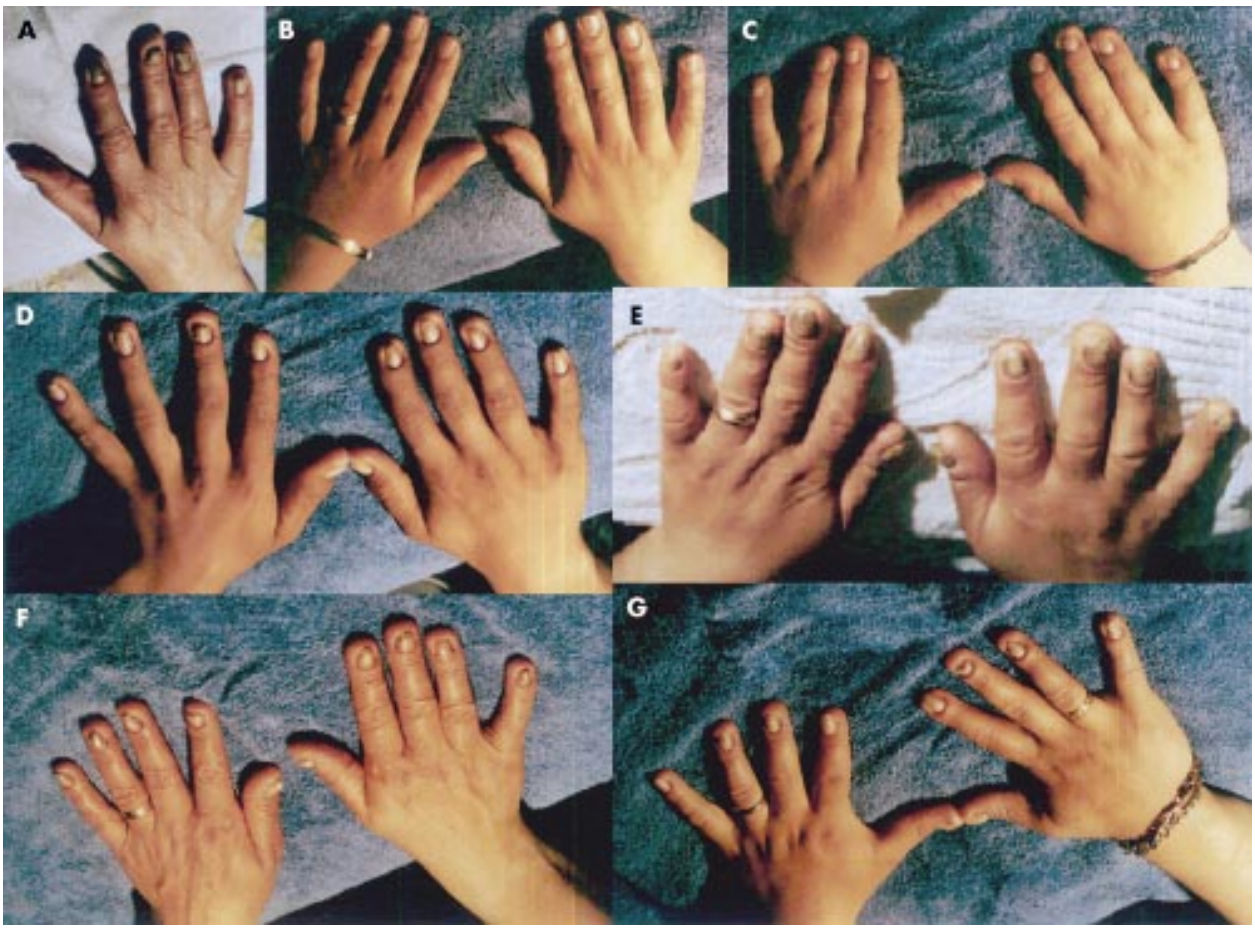

Figure 2 Lesions of the nails of the hands in seven affected family members. (A) V.4, (B) VI.5, (C) VII.2, (D) VI.9, (E) V.7, (F) V.10, (G) VI.7.

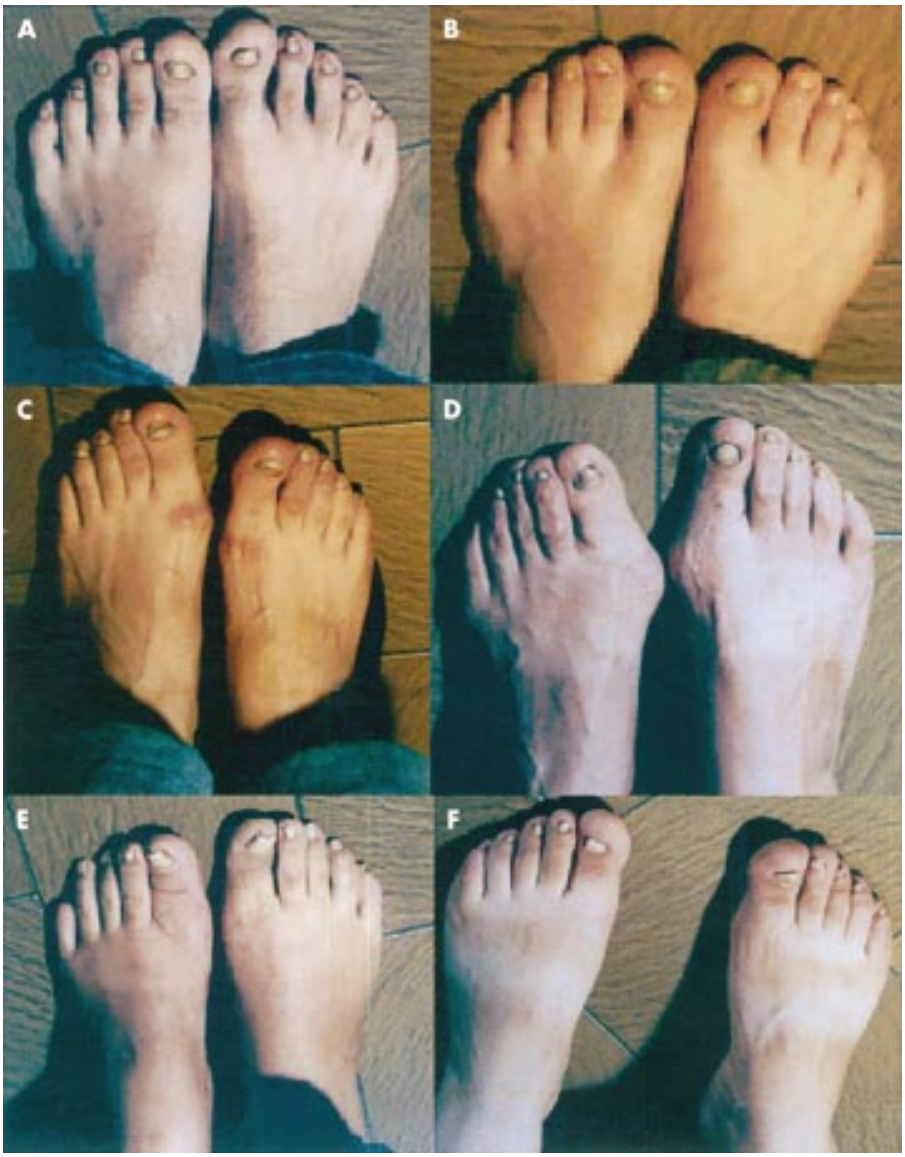

Figure 3 Lesions of the nails of the feet in six affected family members. (A) VI.9, (B) VII.2, (C) V.4, (D) V.7, (E) VI.5, (F) VI.7.

been treated over the years by topical and systemic antimycotic drugs, which resulted in temporary recovery, while never reaching complete remission.

After informed consent, a blood sample was collected from seven affected (V.4, V.7, V.10, VI.5, VI.7, VI.9, VII.2) and 15 unaffected family members (IV.1, IV.4, IV.5, IV.10, V.3, V.6, V.8, V.11, VI.4, VI.10, VI.11, VI.12, VI.13, VI.14, VII.3). Nail specimens from the affected subjects were obtained from lesional and non-lesional sites by cutting and scarifying. All subjects underwent exhaustive tests to investigate possible endocrine abnormalities.[4] Oral and vaginal swabs were collected from all patients. In addition, the autoantibody profile was investigated. Following isolation and culture, Candida strains were characterised and virulence properties evaluated. Confirmation of species identification was performed using API products (BioMerieux, NY). The adhesion of isolates to the HeLa cells was assayed according to Samaranayake and McFarlane.[5] Cell surface hydrophobicity (CSH) was

Table 2 Results of nail microbiological investigations and ICAM-1 assays

Subjects	Involved nails	ICAM-1 concentration (ng/ml)	Species	% CSH*
V.4	Hands and feet	46.80	*C parapsilosis*	85
V.7	Hands and feet	62.10	*C albicans*	77
V.10	Hands and feet	55.60	*C parapsilosis*	90
VI.5	Feet only	79.20	*C albicans*	95
VI.7	Hands and feet	58.00	*C parapsilosis*	82
VI.9	Hands and feet	54.60	*C albicans*	89
VII.2	Hands and feet	86.70	*C albicans*	78

*Cell surface hydrophobicity.

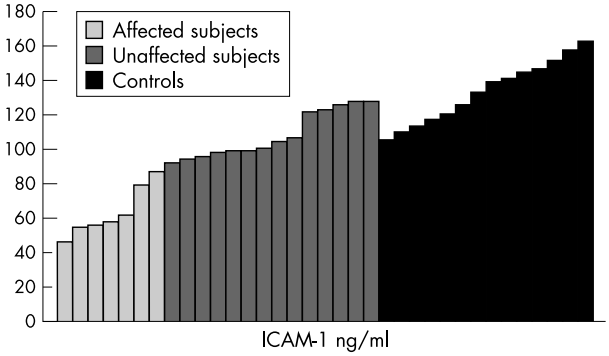

Figure 4 Distribution of ICAM-1 serum concentration in affected subjects, their relatives, and controls.

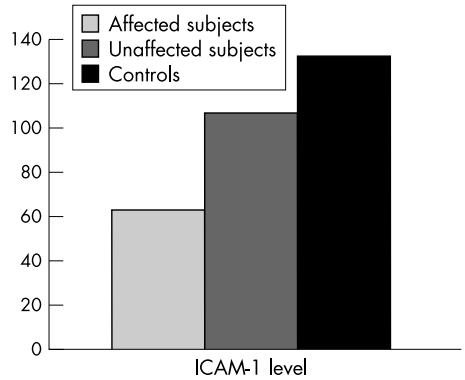

Figure 5 Statistical comparison of mean ICAM-1 level.

determined by the method of Hazen and Hazen[6] at 37°C. Secretory aspartyl proteinase production of isolates was evaluated in solid medium, as reported by De Bernardis *et al*.[7] Serum ICAM-1 levels were assayed on the affected and unaffected family members, and 14 controls, sex and age matched, using anti-ICAM-1s human antibody (Biosourch International, Camarillo, CA, USA). Data, expressed as means (SD), were examined by one way analysis of variance (ANOVA) and the Student-Newman-Keults test.

RESULTS

No autoantibodies were detected in any of the subjects tested. All biochemical investigations showed unremarkable results. Oral and vaginal swabs were negative for Candida infection. Results of nail microbiological investigations and ICAM-1 assays are summarised in table 2. All patients were infected by different kinds of the genus Candida, pointing to inability of the immune system to respond to the antigenic stimulus specific against Candida. The mean ICAM-1 level and concentration (figs 4 and 5) in the affected subjects was 63.29 (SD 14.36) ng/ml, compared to 108.31 (SD 13.57) ng/ml in the unaffected relatives and 133.24 (SD 18.36) ng/ml in the controls (by ANOVA test, $p<0.05$). Routine testing did not show any endocrine or autoimmune disorder in the affected subjects, excluding the APECED form of CMC (table 3).

DISCUSSION

Our pedigree illustrates the vertical transmission of a form of CMC affecting only the nails of the hands and feet, associated with low serum levels of ICAM-1. The mean concentration values of ICAM-1 in the affected subjects was lower than in unaffected relatives and controls. In general, serum ICAM-1

Table 3 Results of routine, endocrine, and autoimmune tests

	V.7	VII.2	V.4	VI.7	VI.9	V.10	VI.5
Endocrinological tests							
TSH (NR 0.4–4 µUI/ml)	0.30	1.8	0.32	0.59	1.50	0.88	1.39
T3 (NR 0.8–1.8 ng/ml)	2.20	1.6	1.4	1.3	1.8	1.5	1.5
T4 (NR 4.5–12.5 µg/ml)	9.8	8.5	9.8	7.6	8.6	10.4	9.2
FT3 (NR 1.8–4.2 pg/ml)	5.3	3.4	3.3	3.3	4.3	3.6	3.8
FT4 (NR 10.3–24.4 pmol/l)	19.4	16.3	18.8	16.1	19	20	15.2
PTH (NR 12–72 pg/ml)	20.6	22.6	55	43.1	19.6	24.2	28.2
Calcitonin (NR 0–20 pg/ml)	8	9	10	10	11.5	12.5	12.5
Hydrocortisone 8:00 am (NR 6.8–26.3 µg/100 ml)	10	11	15	15	12	12	14
Aldosterone (NR 35–300 pg/ml)	46.9	45.8	29.7	30.7	81	56.4	76.4
Prolactin (NR 64–424 µUI/ml)	160	156	118	416	112	419	125
Immunological tests							
AbTGA	Neg	Neg	Neg	Neg	Neg	Neg	Neg
AbTMA	Neg	Neg	Neg	Neg	Neg	Neg	Neg
AbTPO	Neg	Neg	Neg	Neg	Neg	Neg	Neg
AbTSHR	Neg	Neg	Neg	Neg	Neg	Neg	Neg
ANA	Neg	Neg	Neg	Neg	Neg	Neg	Neg
IgG (NR 700–1600 mg/dl)	1500	1600	1480	1380	1480	1100	1650
IgA (NR 70–400mg/dl)	280	250	110	280	110	300	110
IgM (NR 40–230 mg/dl)	99	97	115	125	98	180	105
Biochemical tests							
Azotaemia (NR 10–50 mg/dl)	20	19	22	25	20	33	30
Glycaemia (NR 65–110 mg/dl)	85	80	91	84	85	91	92
Glycosuria	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Blood calcium (NR 8.2–10.4 mg/dl)	9.2	9.5	9.8	9.5	9.2	9.8	9.2
LDH (NR 150–460 U/l)	350	300	360	370	355	305	342
GOT (NR GOT 10–42 U/l)	25	27	28	21	21	23	20
GGT (NR GGT 10–50 U/l)	15	16	10	12	8	13	14
RC (NR men 4 500 000–5 500 000 mmc, woman 4 000 000–4 500 000 mmc)	4 280 000	4 540 000	4 480 000	4 580 000	4 780 000	4 350 000	4 230 000
WC (NR 4500–9000 mmc)	5600	5400	5800	6800	6750	5750	6550
PLT (NR 150 000–350 000 mmc)	26 5000	281 000	252 000	232 000	212 000	250 000	310 000

NR: normal range; TSH: thyroid stimulating hormone; T3: 3-iodine-tyrosine; T4: 4-iodine-tyrosine; FT3: free T3; FT4: free T4; PTH: parathormone; AbTGA: antitireoglobulin antibodies; AbTMA: antimicrosomial antibodies; AbTPO: antiperoxidase antibodies; AbTSHR: anti-TSH receptor antibodies; ANA: antinucleous antibodies; IgG: immunoglobulin type G; IgA: immunoglobulin type A; IgM: immunoglobulin type M; LDH: lactic dehydrogenase; GOT: aspartate-amino-transferase; GGT: γ-glutamil-transpeptidase; RC: red blood cells; WC: white blood cells; PLT: platelet.

levels are increased in chronic inflammatory conditions, in contrast to the affected subjects in the present family. Intercellular adhesion molecule-1 (ICAM-1 or CD54) is a glycoprotein membrane and a member of the immunoglobulin superfamily which plays a central role in cell to cell mediated immune response and is a ligand for leucocyte function associated antigen-1 (LFA-1).[8] ICAM-1 can be expressed by several cell types, including most activated immunocompetent cells,[9 10] fibroblasts,[11] and epithelial cells.[12] Furthermore, surface ICAM-1 expression has been detected in the epithelium in several inflammatory and neoplastic diseases.[13 14] Genetic studies using different types of back cross mice, either protected or not against vaginal candidiasis, after peripheral immunisation, showed that candidate loci for the immune response to vaginal candidiasis included ICAM-1, the ICAM-1 related sequence 1, and the Fc epsilon RII.[15] Genetically engineered mice, lacking ICAM-1 expression, lost more weight and had a significantly higher mortality rate following an intravenous challenge with *Candida albicans* compared to normal wild mice.[16] Based on evidence in the murine models, we investigated ICAM-1 and found decreased values in all affected subjects. Disease inheritance, clinical expression restricted to the nails of the hands and feet, together with decreased ICAM-1 levels point to a distinct form of CMC, familial chronic nail candidiasis with ICAM-1 deficiency (FCNC). In CMCs both autosomal dominant and recessive inheritance models have been reported. Sams *et al*[17] and Jorizzo *et al*[18] reported autosomal dominant transmission of CMC (MIM *114580). Evidence favouring familial autosomal recessive inheritance of CMC (MIM *212050) was discussed by Wells *et al*[1] and Germain *et al*.[19] We were able to trace back the origin of the family to 1689. The pedigree analysis favours autosomal dominant inheritance with incomplete penetrance, even if a few marriages between consanguineous relatives are present.

There is a clear clinical concordance between ICAM-1 serum levels and nail dystrophy. Interestingly, the only unaffected obligate carrier we analysed showed ICAM-1 serum levels (98.00 ng/ml) intermediate between those found in affected (63.29 (SD 14.36) ng/ml) and unaffected non-carrier relatives (108.31 (SD 13.57) ng/ml). However, the pathogenesis of the nail lesions in this family is unclear and the relationship with the reduced ICAM-1 expression awaits clarification.

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