Trichorhinophalangeal syndrome type I and systemic lupus erythematosus with complement C4A homozygous null alleles in the same family

SOLBRITT RANTAPÄÄ DAHLQVIST,¹ BO LUNDSTRÖM,² AND GÖSTA HOLMGREN³

From the Departments of ¹Rheumatology, ²Radiology, and ³Clinical Genetics, University Hospital, Umeå, Sweden

SUMMARY A three generation family from northern Sweden with both trichorhinophalangeal syndrome type I (TRP I) and systemic lupus erythematosus (SLE)-like syndrome with complement C4 homozygous null alleles is described. Five family members in three generations were affected by the TRP I syndrome, indicating autosomal dominant inheritance. Two members had clinical and laboratory signs of SLE and two other members SLE-like syndrome. All living family members in the first and second generation had homozygous C4A null alleles. In three of the adults the two syndromes occurred simultaneously, probably in this family by coincidence.

The trichorhinophalangeal syndrome type I (TRP I) is mainly characterised by sparse, slow growing scalp hair, a pear-shaped broad nose, and short deformed fingers with cone-shaped epiphyses (type 21) of some of the middle phalanges of the hands.¹ Additional features that have also been described include short stature, Perthes-like changes in the hip, short great toes, a long philtrum, a thin upper lip, medially thick and laterally thin eyebrows, pearl-like discoloration of fingernails, prominent ears, and mild micrognathia.^{1,2} Renal and cardiac malformations have also been described in case reports.^{1,2} More than 80 cases with this syndrome have been reported.³

Most cases with TRP I occur in families, and autosomal dominant transmission has been shown for most of them. In a few families only siblings are affected, suggesting a recessive type of transmission or incomplete penetrance of a dominant gene.¹ Solitary cases of TRP I, mostly women, have also been described. In TRP I, in contrast with TRP II, no chromosomal abnormalities have been described.^{4,5} Progressive arthritic symptoms of the thoracic spine, elbows, and fingers in mid-life have been reported without further definition in patients with TRP I.⁶

Patients with deficiency types of certain comple-

ment components, especially those at the beginning of the cascade (C1-C4), have been found to have a higher incidence of systemic lupus erythematosus (SLE).⁷ Deficiency types C4A and C4B are frequently found in patients with SLE.⁸

In this study we report a unique three generation family with TRP I, SLE or SLE-like disease, and homozygous C4A null alleles occurring, we suggest coincidentally in the same family.

Patients and methods

The family, comprising 10 members, originated from northern Sweden (Fig. 1). All except I:1, the proband's father, who is deceased were examined clinically, radiologically, serologically, and cytogenetically. Hospital records of I:1 were studied. He died in 1948 at the age of 45 years owing to acute endocarditis with pancarditis and polyarthritis. His mother had died at the age of 26 and his two sisters died young. There were no signs of the TRP I syndrome or SLE in his father or his half brothers and sisters, according to family history. Patient II:2 was previously examined at another department of rheumatology because of Raynaud's phenomenon and arthralgia.

LABORATORY EXAMINATIONS

Antinuclear antibody was measured by standard techniques (Department of Bacteriology, University

Accepted for publication 6 February 1989.

Correspondence to Dr S Rantapää Dahlqvist, Department of Rheumatology, University Hospital, S-901 85 Umeå, Sweden.

Fig. 1 Pedigree of the family. The complement C4, A and B types, and the HLA haplotypes of A, B, and DR loci are listed for all family members. NT=not tested; X indicates allele unknown owing to lack of antigen specificity or homozygous type; DLE=discoid lupus erythematosus; ANA=antinuclear antibody; TRP I=trichorhinophalangeal syndrome type I.

Hospital, Umeå) in all living members, except III:3 who was too young.

HLA-A, B, and DR typings were performed as previously described⁹ in I:2, II:2-4, III:1-3 at the State Institute for Blood Group Serology, Linköping, Sweden and HLA-A and B typing in II:1 and II:5 at the Blood Center, University Hospital, Umeå, Sweden.

Properdin factor B (Bf), complement C3, and complement C4 types in serum were studied as previously described⁸ in all family members except in I:1. The complement typings were performed at the Department of Medical Genetics, University Hospital, Umeå.

Serum complement C4 was measured by immunodiffusion using partigen plates (Behringwerke AG, Hamburg, West Germany). Normal range of serum C4 was 0.21-0.49 g/l.

CYTOGENETIC EXAMINATIONS

Chromosome analyses were performed on cultured blood lymphocytes in all family members except I:1. High resolution G banding (actinomycin D and trypsin G banding) was used and 11 metaphases were examined.¹⁰

RADIOGRAPHIC EXAMINATIONS

Radiographic examinations of the hands and feet were performed in all living family members and of the hip joints in the three members with clinical symptoms in those joints.

Results and discussion

Figure 1 presents the family pedigree and Tables 1-3 the clinical, radiological, and serological findings of the family members. The clinical and radiological

Table 1 Clinical signs of trichorhinophalangeal syndrome type I and age of the family members

Generation:	I		II					III		
Family member:	1	2	1	2	3	4	5	1	2	3
Age (years)	-	77	53	52	47	46	42	18	16	14
Fine, sparse scalp hair	+	-	-	+	+	-	-	+	+	-
Light coloured hair	+	-	-	+	?	-	-	+	+	-
Sparse eyebrows laterally	?	?	-	+	+	-	?	+	+	-
Bulbous nose	?	-	-	+	+	-	-	+	+	-
Long philtrum	?	-	-	+	+	-	-	+	+	-
Thin upper lip	?	-	-	+	+	-	?	+	+	-
Short stature	+	-	-	+	+	-	-	+	+	-
Short middle phalanges II-V	(+)	-	-	+	+	-	-	+	+	-
Small feet and short great toes	?	-	-	+	+	-	-	+	+	-

Table 2 Clinical signs of systemic lupus erythematosus, Raynaud's phenomenon, antinuclear antibody titre, and C4 concentration

Generation:	I		II					III		
Family member:	I	2	I	2	3	4	5	I	2	3
Discoid lupus	?	—	—	—	+	—	—	—	—	—
Photosensitivity	?	—	—	+	+	—	—	—	—	—
Arthritis	+	—	—	+	—	—	—	Arthralgia	—	—
Pleuritis pericarditis	+	—	—	—	—	TBC*	—	—	—	—
Alopecia	+	—	—	+	+	—	—	(+)	(+)	—
ANA* positivity	?	Neg	Neg	Neg†	1/25	Neg	1/25	Neg	Neg	NT
Raynaud's phenomenon	?	—	—	+	—	—	+	—	—	—
C4 concentration (g/l)	NT*	0.29	0.33	0.38†	0.33	0.30	0.26	0.51	0.24	NT

*ANA=antinuclear antibody; NT=not tested; TBC=tuberculosis.
†During active disease ANA 1/100, nDNA 1/25, and C4 concentration 0.19 g/l.

Table 3 Radiographic findings of the hands, feet, and hips

Generation:	I		II					III		
Family member:	I	2	I	2	3	4	5	I	2	3
Age at (x-ray)	0	77	52	46-52	46	45	42	13-17	15	13
Hands	0	—	—	+	+	—	—	+	+	—
Feet	0	—	ad 3	+	+	ad 3	—	(+)	(+)	—
Hips	0	0	0	ad 1	ad 2	0	0	ad 2	0	0

+ = Typical cone-shaped epiphyses; (+) = short phalanges, not cone-shaped; ad 1 = aseptic necrosis of the femoral head (Perthes disease); ad 2 = small, Perthes-like changes; ad 3 = aseptic necrosis of the head of the second metatarsal (Köhler II disease); — = no changes; 0 = no examinations not performed.

findings in II:2 and 3 and III:1 and 2 were in agreement with previous observations on the TRP I syndrome.⁵ They showed typical changes with cone-shaped epiphyses of the middle phalanges of the fingers (Figs 2 and 3), usually the second and third fingers; in total all eight second fingers and seven of eight third fingers were involved. In the foot, coning was seen in II:2 and II:3, whereas the two other patients III:1 and 2 had short phalanges without coning. Short phalanges without coning were also seen occasionally in the hand, especially the thumb, in all four patients. Three of the four patients (II:2,3, III:1) with typical finger changes also had minor abnormalities of the femoral head, resembling Perthes-like changes. Two other patients (II:1 and II:4), otherwise normal, showed deformities of the second metatarsal head, quite typical for previous aseptic necrosis (Köhler II disease). To the best of our knowledge aseptic necrosis of the second metatarsal head has not previously been mentioned as a symptom in TRP I. On the other hand; these patients (II:1 and II:4) did not have any other skeletal manifestations of TRP I, so this observation may lack significance. In patient III:1 left hydro-nephrosis was diagnosed and stenosis of the ureter was operated on at the age of 15. In 1986 an

operation with osteotomy was carried out on his right hip because of pain.

The inheritance of TRP I in this family was in accordance with autosomal dominant inheritance as reported in most other families. High resolution G-banding of all nine subjects showed normal chromosome complements. In the chromosomal examinations special attention was paid to the region 8q2 on chromosome 8 and to chromosomes 9 and 11. In a sporadic case of TRP I a de novo 9:11 translocation (p22;q21) has been described.¹¹ In several cases of TRP II deletion, terminal or interstitial, in the distal region of chromosome 8 with the critical segments to 8q22-q24 has been reported.^{4, 12} Cases of TRP I have been sporadic and they differ from TRP I by the presence of mental retardation and multiple cartilaginous exostoses.

The father (I:1) had symmetric peripheral polyarthritides, myalgia, and fever at the age of 43 and four years before that pleuritis. Treatment with gold injections and sulphasalazine was tried but was discontinued because of side effects. The disease engaged the joints of the elbows, shoulders, hips and ankles. Gradually the patient developed pleuritis and pericarditis and died owing to acute endocarditis 1½ years after the disease onset. He

Fig. 2 Patient II:2 with cone-shaped epiphyses of the bases of the middle phalanges of the second and third finger caused by premature closure of the central ulnar portion of the growth plate. (The third finger is shown.)

Fig. 3 Patient III:2. Cone-shaped epiphyses in trichorhinophalangeal syndrome. All middle phalanges of the fingers are short as well as the distal phalange of the thumb. No coning in the thumb.

erythrocyte sedimentation rate was greatly increased (37–167 mm/h). Neither serological examination nor radiology of the hands or feet was performed. From the description by his children and according to the hospital records it appears that I:1 probably had the TRP I syndrome (Table 1).

The proband (II:2) had had arthralgia and a raised erythrocyte sedimentation rate for about 20 years. During the past years she has had arthritis of the metacarpophalangeal, metatarsophalangeal,

ankle, knee, and elbow joints, photosensitivity, and Raynaud's phenomenon. During active disease she was antinuclear antibody positive 1/100 (homogen), nDNA positive 1/25, and C4 concentration was lowered to 0.19 g/l. She fulfilled the American Rheumatism Association criteria for SLE.¹³ She was successfully treated with corticosteroids and chloroquine.

The only brother with the TRP syndrome (II:3) had had discoid lupus, photosensitivity for 10–15 years and a low titre of antinuclear antibody, but he has had no arthritis so far. Brother II:5 had Raynaud's phenomenon and arthralgia and a low titre of antinuclear antibody. These symptoms appeared gradually over the past few years. He had no symptoms of TRP I (Table 1).

Complement typings showed that I:2 and all her children II:1–5 were homozygous for the C4A null genes (see Fig. 1). Patient I:1 must at least have had heterozygote C4A null allele. At least one C4 null

allele was in linkage disequilibrium with HLA-B8, DR3. Patients I:2, II:1, and II:5 had no symptoms or signs of an inflammatory joint disease despite homozygous C4 AQ0 genes. In this family three out of six individuals with homozygous C4A null alleles had clinical and laboratory findings of SLE or SLE-like disease. C4 concentration was normal in all family members except in the proband during active disease. None of the syndromes was associated with Bf or a complement C3 type.

In conclusion, the present family coincidentally seem to have two syndromes: TRP I and SLE or SLE-like disease with homozygous C4 null alleles. A linkage of the two syndromes or postulation of a new syndrome is contradicted by the observation that one individual (II:5), who had homozygous C4A null alleles and symptoms of an SLE-like syndrome, did not show any clinical signs of TRP I. Moreover, the two eldest sons of the proband (III:1, 2) had symptoms of TRP I but do not have SLE or SLE-like symptoms so far. They have C4A heterozygous null allele.

This work was supported by grants from the Medical Faculty, University of Umeå. Mrs Gun-Britt Johansson and Ms Carin Hiort are gratefully acknowledged for excellent technical assistance.

References

- 1 Giedion A, Burdea M, Fruchter Z, Meloni T. Autosomal-

- dominant transmission of the tricho-rhino-phalangeal syndrome. Report of 4 unrelated families, review of 60 cases. *Helv Paediatr Acta* 1973; **28**: 249-59.
- 2 Weaver D D, Cohen M, Smith D W. The tricho-rhinophalangeal syndrome. *J Med Genet* 1974; **11**: 312-4.
- 3 Giedion A. Acrocysplasias. Peripheral dysostosis, acrodysostosis and Thiemann's disease. *Clin Orthop* 1976; **114**: 107-15.
- 4 Bühler E M, Bühler U K, Clinsten R. Terminal or interstitial deletion in chromosome 8 long arm in Langer-Giedion syndrome (TRP II syndrome)? *Hum Genet* 1983; **64**: 163-6.
- 5 Noltorp S, Kristoffersson U, Mandahl N, Stigsson L, Svensson B, Werner C-O. Trichorhinophalangeal syndrome type I: symptoms and signs, radiology and genetics. *Ann Rheum Dis* 1986; **45**: 31-6.
- 6 Beals R K. Tricho-rhino-phalangeal dysplasia. Report of a kindred. *J Bone Joint Surg [Am]* 1973; **55**: 821-6.
- 7 Rynes R I. Inherited complement deficiency states and SLE. *Clin Rheum Dis* 1982; **8**: 29-47.
- 8 Rantapää Dahlqvist S, Beckman G, Beckman L. Serum protein markers in systemic lupus erythematosus. *Hum Hered* 1988; **38**: 44-7.
- 9 Hägglöf B, Holmgren G, Holmlund G, Lindblom B, Olaisen B, Tersberg P. Studies of HLA, factor B (Bf), complement C2 and C4 haplotypes in type I diabetic and control families from northern Sweden. *Hum Hered* 1986; **36**: 201-12.
- 10 Verma R S, Lubs H A. A simple R banding technic. *Am J Hum Genet* 1975; **27**: 110-7.
- 11 Booth C W, Mauer W F. De novo 9:11 translocation in a sporadic case of trichorhinophalangeal (I) syndrome. [Abstract] *Pediatr Res* 1981; **15**: 559.
- 12 Fryns J P, Heremans G, Marien J, van den Blighe H. Langer-Giedion syndrome and deletion of the long arm of chromosome 8. Confirmation of the critical segment to 8q23. *Hum Genet* 1983; **64**: 194-5.
- 13 Tan E M, Cohen A S, Fries J F, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271-7.