Palmoplantar keratoderma, nail dystrophy, and hereditary motor and sensory neuropathy: an autosomal dominant trait

J L TOLMIE*, D E WILCOX*, R McWILLIAM†, A ASSINDI†, AND J B P STEPHENSON†

From *the Duncan Guthrie Institute of Medical Genetics, and †Fraser of Allander Unit of Paediatric Neurology, The Royal Hospital for Sick Children, Glasgow G3 8SJ.

SUMMARY Autosomal dominant inheritance of a syndrome comprising palmoplantar keratoderma, nail dystrophy, and hereditary motor and sensory neuropathy (HMSN) was observed in three generations of one family. Nail dystrophy affected the toe and fingernails; it was present at birth or developed during early childhood. Palmoplantar keratoderma became apparent in later childhood. Each subject with nail dystrophy and keratoderma also had clinical or electrophysiological evidence of axonal neuropathy.

Extensive genetic heterogeneity is present in the hereditary motor and sensory neuropathies (HMSN) and palmoplantar keratodermas (PPK). They occur as dominant, recessive, or sex linked traits, and also with other abnormalities in a variety of rare inherited syndromes.^{1 2} We report a Scottish

family in which an autosomal dominant syndrome of nail dystrophy, HMSN, and PPK is segregating.

Case reports

The proband (V.1, fig 1) first walked at the age of 17 months. Her gait was unusual and lower limb spasticity was thought to be present. Plantar fas-

FIG 1 Family pedigree. A horizontal bar above the symbol denotes subjects clinically assessed by the authors. It was not possible to ascertain who was affected in the first generation.

Received for publication 5 November 1987.

Revised version accepted for publication 5 January 1988.

ciotomies were performed at the age of four years. By the age of eight years talipes equinovarus was present. Bilateral Steindler procedures were unsuccessful in lengthening the arches of her feet. Nail dystrophy and PPK were noted at three years and 10 years respectively. Examination at the age of 15 years showed clinically normal sensory function, absent knee jerks, retained ankle jerks, and extensor plantar responses, but no spasticity was detected. The sensory nerve action potential (SAP) was undetectable in the sural nerve. The motor nerve conduction velocity (MNCV) could not be estimated because the common peroneal nerve was not able to be stimulated at an acceptable amplitude level. Muscle biopsies were obtained from both feet and histochemical examination showed many fibres in large areas to be of a single fibre type, implying extensive reinnervation after partial denervation.

II.2, III.3, and III.4 were reported to have had keratoderma and nail dystrophy. II.2 and III.3 were remembered as having suffered cramping muscular pains in their calves at night. None of these persons

was thought to have had signs of motor disability during life.

III.2 was examined at the age of 56 years. She developed dry, thickened skin on her palms and soles with horizontal cracks on the outer third of the palmar creases at around 12 years of age. Her nails were thickened with pitting and vertical ridging which was less severe than in her son, IV.2. Her gait was normal and there was no muscle wasting, but she had mild pes cavus deformity and reduced ankle jerks. Sensory testing was normal, ankle jerks were diminished, and plantar responses were flexor. The SAP was absent in the median, ulnar, and sural nerves; MNCVs were 41 and 44 m/sec in the common peroneal and ulnar nerves.

IV.2 attended hospital during childhood because of intoeing which corrected spontaneously. Palmo-plantar keratoderma and nail dystrophy were noted in early childhood. At the age of 40 years he has mild pes cavus, keratoderma with circular callosities on his soles and palms, and severely dystrophic nails with painful, longitudinal cracks (fig 2). His knee

FIG 2 Nail dystrophy and keratoderma affecting subject IV.2.

jerks were exaggerated and ankle jerks diminished. Plantar responses were flexor. No SAP was detected in the sural nerve and the MNCV in the common peroneal nerve was slightly reduced at 40 m/sec.

IV.4 had tendon transfer operations for bilateral pes cavus at the age of 11 years. Keratoderma and nail dystrophy were present at that time. At 43 years he has marked pes cavus deformity, despite which he was able to complete an arduous 90 mile cross country hike. Knee jerks were present but ankle reflexes were diminished. Plantar responses were flexor. The MNCV was marginally reduced and there was absence of the SAP in the sural and median nerves. Electromyography of the tibialis anterior and extensor digitorum communis muscles showed neuropathic features.

V.2 was examined at the age of seven years. Nail dystrophy was present from six months but keratoderma was not evident. He walked at 18 months and a tendency to toe walk was corrected by a brief spell in below knee plasters. Clinical neurological examination was normal. The MNCV in the common peroneal nerve was reduced at 39 m/sec and the SAP was not detected in the sural nerve.

V.6 was examined at the age of six years. Nail dystrophy affected the fingers more than the toes and keratoderma was evident on the palms. Neurological examination was normal but again the MNCV was marginally reduced with absence of the sural and median SAP.

V.8 was noted to have nail dystrophy at birth. She was born by caesarean section because of breech presentation. She walked at the age of 13 months when congenital dislocation of the left hip was diagnosed. Examination at that time revealed areflexia and the MNCV in the common peroneal nerve

was 45 m/sec. A muscle biopsy at the time of open reduction of her hip was normal in appearance.

OTHER INVESTIGATIONS

Normal Giemsa banded karyotypes were obtained from peripheral blood lymphocytes of subjects IV.2 and V.1. Flow karyotypes³ were also normal from IV.2, his healthy spouse, and their affected daughter. Two clinically unaffected adults, IV.1 and IV.3, had nerve conduction studies performed which gave normal results. Unaffected children were not subjected to electrophysiological tests.

Discussion

The syndrome exhibits variable expression. At the age of 60 years II.2 had no symptoms attributable to her neuropathy but moderately severe pes cavus was present in her son and nephew. Walking was not significantly impaired in these persons. Nail dystrophy was documented at birth in V.8, while the youngest age at which keratoderma was noted was six years. The nail dystrophy was most severe in IV.2 (fig 2) where its clinical appearance and quality suggested lichen planus. However, a nail biopsy, including matrix tissue, was not considered justified to investigate this. The keratoderma comprised punctate lesions on abnormal surrounding skin. It is worth noting that punctate keratoderma and nail dystrophy without HMSN is a recognised autosomal dominant trait.²

The marginal slowing of MNCV with absence of SAP in asymptomatic and symptomatic affected subjects, the neuropathic EMG in IV.4, and the muscle biopsy findings in V.1 strongly suggest an underlying axonal neuropathy. The clinical evidence

FIG 3 *Pes cavus deformity affecting V.1.*

of pyramidal tract dysfunction in cases V.1 and IV.2 was interesting as it suggests the syndrome of peroneal muscular dystrophy with pyramidal signs, a distinct autosomal dominant trait not known to be associated with dermatological abnormalities.⁴

A similar autosomal dominant condition to the one reported here was present in an Italian family with palmoplantar keratoderma and Charcot-Marie-Tooth disease.⁵ The clinical and electrophysiological findings were thought to indicate an axonal neuropathy. However, nail dystrophy was not noted in that report whereas it was a constant finding among the affected subjects we examined. We therefore believe that these conditions are distinct.

Two families have been described in which keratoderma and spastic paraplegia were inherited together. The first⁶ comprised four brothers with mental retardation, spastic paraplegia, pes cavus, striate keratoderma of the palms, and diffuse hyperkeratosis of the soles. The normally intelligent mother of these men had abnormal nails, hyperkeratosis of the soles, and slight clawing of the toes; sex linked inheritance was thought likely. Nerve conduction studies were not reported.

In the second family,⁷ autosomal dominant inheritance of a distinctive keratoderma with spastic paraplegia occurred. Extensor plantar responses and increased reflexes were present and focal hyperkeratotic papulonodules were present on the palms and soles. Nail dystrophy was not noted in

any persons; thus we feel that on available evidence this condition is distinct from the one we report.

We thank Professor Rona MacKie of the Department of Dermatology, the University of Glasgow, and Dr Andrew Weir of the Institute of Neurological Sciences, Glasgow, for advice; and Dr David Doyle of The Institute of Neurological Sciences, for interpreting the muscle biopsies.

References

- ¹ Baraitser M. *The genetics of neurological disorders*. Revised ed. Oxford: Oxford University Press, 1985:165-78.
- ² Rook A, Wilkinson DS, Ebling FJG, eds. *Textbook of dermatology*. Vol 2. Edinburgh: Blackwell Scientific Publications, 1979:1300-14.
- ³ Harris P, Boyd E, Young BD, Ferguson-Smith MA. Determination of the DNA content of human chromosomes by flow cytometry. *Cytogenet Cell Genet* 1984;**41**:14-21.
- ⁴ Harding AE, Thomas PK. Peroneal muscular atrophy with pyramidal features. *J Neurol Neurosurg Psychiatry* 1984;**47**:168-72.
- ⁵ Rabbiosi G, Borroni G, Pinelli P, Cosi V. Palmoplantar keratoderma and Charcot-Marie-Tooth disease. *Arch Dermatol* 1980;**116**:789-90.
- ⁶ Fitzsimmons JS, Fitzsimmons EM, McLachlan JM, Gilbert GB. Four brothers with mental retardation, spastic paraplegia and palmoplantar hyperkeratosis. A new syndrome? *Clin Genet* 1983;**23**:329-35.
- ⁷ Powell FC, Venecie PY, Gordon H, Winkelmann RK. Keratoderma and spastic paralysis. *Br J Dermatol* 1983;**109**:589-96.

Correspondence and requests for reprints to Dr J L Tolmie, Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow G3 8SJ.