Naevoid basal cell carcinoma syndrome and Charcot-Marie-Tooth disease

Two autosomal dominant disorders segregating in a family¹

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SUMMARY A family is described in which 16 individuals in 3 generations have Charcot-Marie-Tooth disease. At least 6 family members also have the naevoid basal cell carcinoma syndrome. In addition, 1 subject with both disorders has 2 young daughters with the naevoid basal cell carcinoma syndrome.

This family was originally described by Swift and Horowitz (1969) as a family with Charcot-Marie-Tooth disease and jaw cysts. We have recently had the opportunity to study 4 individuals who had participated in the Swift and Horowitz study. In addition, we have examined 3 children born after the previous study. Swift and Horowitz considered the possibility that 'the association of these clinical findings could be fortuitous...or could be a consequence of the pleomorphic effects of a single gene segregating in this family.' This report has been prepared with new evidence to confirm that 2 autosomal dominant diseases, Charcot-Marie-Tooth disease and the naevoid basal cell carcinoma syndrome, are segregating in this kindred. The 2 disorders have not previously been described in the same patient or in the same family.

Report of a family

ASCERTAINMENT

The proband, age 7, was examined by one of the authors (E.F.) because of jaw pain and swelling and subsequently admitted to this institution where an odontogenic kerotocyst was excised. Because the proband and her mother had signs of the naevoid

basal cell carcinoma syndrome, the family was referred for genetic counselling. The mother reported that several family members had previously been examined for jaw cysts. At a genetic counselling conference attended by the proband's mother, maternal grandmother, maternal uncle, and his wife, the genetic counsellor (A.H.) learned while recording the pedigree (Fig.) that the earlier investigations at another institution had included electrodiagnostic studies. It was apparent that some problem other than jaw cysts was investigated at that time. With some probing, it was revealed that several individuals in this family had Charcot-Marie-Tooth disease and that many of them were known to have had jaw cysts and other features of the naevoid basal cell carcinoma syndrome. A family physician informed us that the family had been the subject of a published report, and we eventually uncovered the Swift and Horowitz report. The family members with whom we had contact were not aware of the extensive manifestations of the naevoid basal cell carcinoma syndrome, that there were 2 separate genetic disorders within the family, or that both disorders were transmitted as autosomal dominant traits.

Methods and material

As a result of the genetic counselling provided to this family, 7 family members submitted to physical and/or radiological evaluation and provided access to

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Fig. Family pedigree—1975.

medical records. In addition, medical records were obtained on 1 relative (IV.10) who was not examined by the authors. Electrodiagnostic studies for the current study were done at the same laboratory as that described in the Swift and Horowitz report. The diagnosis of Charcot-Marie-Tooth disease was accepted on the basis of reports from Joseph Goodgold who performed all the electrodiagnostic testing. The diagnosis of naevoid basal cell carcinoma syndrome was based on evidence available from many sources: examination by 2 of the authors (E.F. and A.R.) or a medical geneticist, and reports obtained from pathologists, dermatologists, radiologists, and others who had examined family members. The identification of basal cell carcinoma and specific tumours has been confirmed in each case on the basis of pathology reports. Intelligence is normal in all family members studied.

CLINICAL FEATURES

VI.1

The proband, age 7, had the following history: medulloblastoma excised at age 2 by one of the authors (A.R.), followed by radiotherapy and chemotherapy; 18 months later numerous basal cell carcinomas appeared on the neck, upper abdomen, and lower chest; ovarian fibroma at age 5; a few suggestive pits

of the palms and soles; anomalous widening of the left third rib with a probable incomplete bony fusion between the second and third ribs; small twelfth rib bilaterally; exostoses of the third left rib; spina bifida occulta C6-T1, calcification of the falx cerebri, and an odontogenic keratocyst. There was a ventriculoatrial shunt in place for communicating hydrocephalus secondary to craniotomy. She had a round face, frontal parietal bossing, mandibular prognathism, and hypertelorism.

VI.2

The younger sister, age 4, of the proband developed basal cell carcinoma around the umbilicus at age 4. Calcium deposits were seen in the falx cerebri. A jaw bone cyst was removed at age 5 years. She had amblyopia. Radiological evaluation of the chest and long bones was normal. She did not have the facial characteristics of the naevoid basal cell carcinoma syndrome.

VI.3

The mother, age 35, had a history of multiple jaw cysts from age 8 years to late adolescence. Heavy calcifications of the falx cerebri were noted at 12 years. At age 29 she developed basal cell carcinomas on her nose, arms, and back. Radiological exam-

ination of the chest and long bones was normal. She was an obese woman with a round face, frontal parietal bossing, coarse features, mandibular prognathism, and hypertelorism. The diagnosis of Charcot-Marie-Tooth disease was confirmed by electrodiagnostic studies at age 21.

IV.8

The maternal grandfather, age 59, had an operation for a large, dentigerous, multilocular cyst of the mandible at age 45. There was no history of jaw cysts before age 45. He had heavy calcification of the falx cerebri and scoliosis. At age 58 he had benign acanthoma or solar keratosis, pits of the palms and soles, and multiple basal cell carcinomas of the face and trunk which had not been present on examination by the same dermatologist one year before. He was moderately obese with coarse facial features, mandibular prognathism, and hypertelorism. He had had difficulty walking and running since childhood. Diagnosis of Charcot-Marie-Tooth disease was well documented clinically and by electrodiagnostic studies by 52 years and was advanced at the time of examination.

IV.10

The proband's maternal great-aunt, age 53, had three dentigerous jaw cysts removed from the mandible and maxilla by age 47. There was calcification of the falx cerebri. Basal cell carcinomas appeared at about the age of 50 on the scalp, face, and trunk. Her facial appearance was not characteristic of the naevoid basal cell carcinoma syndrome. Charcot-Marie-Tooth disease was diagnosed by electrodiagnostic studies at the age of 47.

V.4

The maternal uncle, age 28, had none of the features of the naevoid basal cell carcinoma syndrome after dermatological examination and panographic, spinal, rib, and skull x-rays done just before this report. Swift and Horowitz felt that he probably had Charcot-Marie-Tooth disease at age 21 because of slight weakness in dorsiflexing his feet and nerve conduction velocities in the legs, which were just below the lower limit of normal. Recently, electrodiagnostic examination showed no evidence of deterioration by comparison with the previous studies and Dr Goodgold's interpretation of these results rules against the diagnosis of Charcot-Marie-Tooth disease.

VI.3

The son of V.4, age 5 years, had had panographic, chest, and skull x-rays, which were normal. He had no clinical signs of naevoid basal cell carcinoma syndrome or Charcot-Marie-Tooth disease.

V.5

Another maternal uncle, age 25, had no clinical signs of naevoid basal cell carcinoma syndrome or Charcot-Marie-Tooth disease. Electrodiagnostic studies at the time of the Swift and Horowitz report were normal and have not been repeated. He refused radiological evaluation.

Discussion

The naevoid basal cell carcinoma syndrome is a rare disorder characterised by multiple basal cell carcinomas, odontogenic keratocysts, pitting of the palms and soles, ectopic lamellar calcification in the falx cerebri, developmental anomalies of the skull, spine, ribs, and extremities, and characteristic facies. The syndrome is inherited as an autosomal dominant trait with almost complete penetrance and variable expressivity. Multiple jaw cysts and pits of the palms and soles usually develop in childhood; basal cell carcinoma usually appears by the third decade (Gorlin *et al.*, 1965).

Charcot-Marie-Tooth disease is commonly known as peroneal muscular atrophy (Charcot and Marie, 1886; Tooth, 1886). Three types of inheritance are involved; autosomal dominant in about 70% of cases, autosomal recessive, and, less frequently, sex-linked recessive. Onset of symptoms can occur early in childhood or as late as the seventh decade (Bell, 1935; Skyre, 1974).

Of the 29 family members examined by Swift and Horowitz, 16 had evidence of Charcot-Marie-Tooth disease clinically and by electrodiagnostic tests. Of these 16 individuals, 5 had moderate to heavy lamellar calcifications of the falx cerebri and jaw cysts; several had faint calcifications but no jaw cysts.

Swift and Horowitz noted the high frequency of calcification of the falx cerebri and familial cases of jaw cysts in the naevoid basal cell carcinoma syndrome. They did not confirm the diagnosis of the naevoid basal cell carcinoma syndrome in individuals in this family who were found to have these symptoms, because naevi had not appeared though some individuals were more than 50 years of age. Basal cell carcinomas have now been confirmed in IV.8, IV.10, and V.3, and in VI.1 and VI.2, the offspring of V.3. It is now possible to document the association of Charcot-Marie-Tooth disease and the naevoid basal cell carcinoma syndrome in several members of the kindred. In this kindred lamellar calcifications, jaw cysts, and naevi have not been observed in any individual who did not have Charcot-Marie-Tooth disease, except for the 2 young children, VI.1 and VI.2, who could still develop Charcot-Marie-Tooth disease.

The proband, VI.1, is one of two known female

survivors of medulloblastoma with this syndrome. Both patients were treated with radiation therapy after surgery and developed multiple basal cell carcinoma along the radiated field within 6 months to 3 years. Both patients developed prepubertal ovarian fibromas after radiation (Strong, 1977).

The gene for the naevoid basal cell carcinoma syndrome has shown possible linkage to the Rh blood group locus on chromosome 1 (Anderson, 1968). Linkage studies are now in progress on kindred members in co-operation with Louise C. Strong. These studies could produce evidence of value for genetic counselling and prenatal diagnosis of Charcot-Marie-Tooth disease and the naevoid basal cell carcinoma syndrome.

Since the features of the naevoid basal cell carcinoma syndrome occur with great variability, the diagnosis should be considered in any individual with recurrent dentigerous cysts at an early age. The skeletal anomalies are congenital. A thorough radiological evaluation should be done to obtain additional evidence for or against the diagnosis. Early identification of individuals carrying this gene is important in order to monitor for malignancy and for genetic counselling for the family.

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