Coincidence of neurofibromatosis and myotonic dystrophy in a kindred

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SUMMARY Neurofibromatosis and myotonic dystrophy have occurred in ten members of a non-consanguineous family with a high degree of concordance. The expression of neurofibromatosis is peripheral, and the expression of myotonic dystrophy has produced at least moderately severe disability. Neither disease has appeared to alter the phenotypic expression of the other when both have occurred simultaneously. Secretor typing supports the assumption that the myotonic dystrophy in this family is the commonly recognised secretor-linked entity. The segregation pattern of the two disorders in this family suggests the possibility of close linkage between the loci for neurofibromatosis and myotonic dystrophy.

Neurofibromatosis (NF) is an autosomal dominantly inherited disorder with a wide spectrum of manifestations. It is a common single gene disorder, having a prevalence of approximately 30 cases per 100 000 persons.¹ Neurofibromatosis has been reported to occur in subjects with other hereditary neurological disorders, including progressive muscular dystrophy,² Huntington's disease,³ peroneal muscular atrophy,⁴ and Von Hippel-Landau's disease.⁵ Only two previous reports have described single subjects in whom signs of NF and myotonic dystrophy coexist.^{6,7}

Myotonic dystrophy (MD) is also an autosomal dominantly inherited disorder with a variety of manifestations. It has a prevalence of 5 in 100 000⁸ and is perhaps the most common muscular dystrophy of adult life. With the exception of the two single case reports noted above, it has not been noted to occur in association with inherited neurological disorders. Although the central nervous system and the peripheral nervous system do have demonstrated abnormalities, the neurocutaneous phenomena and malignancies characteristic of NF are not features of MD.

We report a kindred with subjects with both NF and MD. This family is unusual not only for the rare coincidence of the two diseases, but also because both NF and MD occurred in seven of nine persons affected with either disorder.

Case reports

A pedigree of the family is presented in the figure; the proband is II·1. The members of the family interviewed and examined by the authors are indicated in the figure. Descriptions of deceased and unavailable persons were obtained from family members. Six café-au-lait spots were minimal criteria for a diagnosis of NF.⁹ Clinical examination as well as electromyography (EMG) were used in the diagnosis of MD. A tabulation of the clinical features of the affected subjects is presented in the table. The family was typed for HLA, the Lutheran blood group, and ABH secretor status.

GENERATION I

I·1 had multiple brown spots recognised from childhood. At the age of 65, she was admitted to hospital and noted to have severe kyphoscoliosis, advanced osteoporosis, and multiple compression fractures of the spine. She was described by her children as having wasting of the temporalis muscles and an unsmiling face. She died at the age of 67. Records indicated that she had NF proved by biopsy and café-au-lait spots. No comments about MD or EMG reports were found in her medical records. She had seven sibs, none of whom was reported to have the signs and symptoms of either NF or MD.

I·2 was diagnosed as having general paresis at the age of 42 in 1931. He was in hospital from the

FIGURE Pedigree of family.

TABLE Clinical features of affected members

Generation	I		II			III					IV	
Case	1	2	1	4	5	3	6	8	11	12	5	7
Age at death/age at onset of MD or NF	67/?	75/?	52/47	37/?	50/46	24/?	22/?	21/?	27/13	24/10	1/1	2/1
Features of MD												
Myotonia	?	?	+	?	+	+	+	+	+	+	-	+
Muscle atrophy	+	?	+	?	+	+	+	+	+	+	-	-
Muscle weakness	+	?	+	+	+	+	+	+	+	+	-	+
Frontal balding	?	?	+	?	+	-	-	+	-	-	-	-
Cataract	-	+	+	?	+	+	-	-	-	-	-	-
Mental retardation	-	-	-	?	-	+	-	+	-	-	-	+
Gonadal atrophy	-	-	-	?	-	+	-	-	-	-	-	-
Cardiomyopathy	-	-	+	?	+	-	-	-	-	-	-	-
Congenital anomaly	-	-	-	?	-	+	-	-	-	-	-	-
Diabetes	-	-	-	?	-	-	-	-	-	-	-	-
Features of NF												
Café-au-lait spots	+	-	+	+	+	+	+	+	+	+	+	-
Neurofibromata	+	-	+	+	+	+	+	-	+	+	-	-
Scoliosis	+	-	-	+	-	+	+	-	-	-	-	-
Mental retardation	-	-	-	-	-	+	-	+	-	-	-	+
Neoplasm (CNS)	-	-	-	-	-	-	-	-	-	-	-	-

age of 51 until his death for dementia secondary to general paresis. He had a cataract of the right eye. He died at age 75 of pulmonary emboli. He had one sister who was reported to be normal. However, that woman's son is reported to be dysarthric, and her daughter developed bilateral cataracts after the age of 40.

GENERATION II

II-1, aged 52, has multiple subcutaneous nodules and café-au-lait spots from childhood. Dysarthria, dysphagia, and mild weakness of the neck and hands began in his 40s. On physical examination, he has peripheral neurofibromata and café-au-lait spots, a

cataract in his left lens, and frontal balding. He also has facial diplegia, temporalis muscle wasting, nasal speech, weak gag reflex, percussion myotonia, and mild weakness in the neck and distal extremities. An EMG revealed myotonic potentials.

II-3 drowned at the age of 4.

II-4 died at the age of 37 of obstructive jaundice. Diffuse pulmonary fibrosis was noted at the age of 24. At the age of 33 he developed pulmonary tuberculosis. Medical records indicated he had a bone cyst in his scapula, café-au-lait spots, and subcutaneous nodules. The diagnosis of NF was confirmed at necropsy. His relatives report he had an unsmiling face and a flapping weakness of his hands.

II-5, a 50-year-old man, was admitted to the State University Hospital in 1974 for progressive dysarthria and dysphagia. Cutaneous examination demonstrated numerous neurofibromata and café-au-lait spots. He had bilateral cataracts as well as facial diplegia, nasal speech, mild proximal weakness, and a moderately severe weakness of the neck flexors. There was percussion myotonia. An EMG of the thenar eminence revealed myotonic potentials with mild denervation activity and polyphasic units. Computed tomography of the brain was normal.

GENERATION III

III-2, a 28-year-old man, has one café-au-lait spot (3×3 cm), but no evidence of NF or MD was noted on physical examination.

III-3, aged 24, is moderately retarded. On examination, he had several congenital anomalies including low set ears, high arched palate, microphthalmia, severe kyphoscoliosis, bilateral cataracts, testicular atrophy, facial diplegia, and temporalis muscle wasting. Multiple café-au-lait spots and subcutaneous nodules were also noted. On neurological examination, facial diplegia, severe dysarthria with nasal speech, marked percussion myotonia, and mild grip myotonia were demonstrated. His EMG was consistent with MD.

III-4, a 22-year-old woman, has no evidence of either MD or NF.

III-6, aged 22, has multiple cutaneous brown spots and nodules noted from childhood. On examination, these were found to be café-au-lait spots and subcutaneous neurofibromata. He had no cataracts or frontal balding. However, there was marked scoliosis, mild neck flexor weakness, atrophy of the sternocleidomastoid muscles, and a suggestion of percussion myotonia. An EMG demonstrated myotonic potentials.

III-8, a 21-year-old man, has always been noted to have significantly delayed psychomotor development. Many café-au-lait spots were present over his trunk and extremities. Frontal balding, temporalis muscle wasting, and percussion myotonia were present. An EMG revealed myotonic potentials.

III-9, aged 19, has two small café-au-lait spots less than 2 cm in diameter. His physical examination was otherwise negative for NF and MD.

III-10, aged 29, presents no evidence of MD or NF.

III-11, a 27-year-old woman, has multiple cutaneous brown spots and a few cutaneous soft lumps noted from childhood. She recalled difficulty in opening her fist at the age of 13 and mild hand weakness at the age of 22. On physical examination, she had multiple café-au-lait spots and two subcutaneous nodules. Facial diplegia, temporalis

muscle wasting, and nasal speech were present on neurological examination. In addition, her examination revealed percussion and grip myotonia as well as weakness of the proximal upper extremities.

III-12, aged 24, has multiple cutaneous brown spots. At the age of 10, she began having trouble opening her fist. An evaluation at the State University Hospital at the age of 23 for epigastric pain recorded the presence of multiple café-au-lait spots, subcutaneous nodules, facial diplegia, temporalis muscle atrophy, nasal speech, and both proximal and mild distal upper extremity weakness. Percussion and grip myotonia were also present. An EMG done at that time was consistent with myotonic muscular dystrophy. A barium swallow showed oesophageal dysmotility.

GENERATION IV

IV-2, IV-3, and IV-4, sibs aged 4, 3, and 1, had no evidence of NF or MD.

IV-5, aged 1, has 10 café-au-lait spots. He has no subcutaneous nodules. There was no clinical evidence of MD.

IV-6, a 3-year-old girl, has no evidence of NF or MD.

IV-7, aged 2, has a high arched palate and is mildly retarded. An EMG revealed myotonic potentials. No café-au-lait spots or subcutaneous neurofibromata were seen.

Results

The NF in this family is of the peripheral type presenting as a combination of café-au-lait spots and neurofibromata. The one boy (IV-7) in whom MD appeared alone may yet develop NF since cutaneous manifestations may not appear until puberty.¹⁰ Myotonic dystrophy in this family demonstrates almost the full spectrum of this disorder, from isolated cataracts of adult onset (I-2) to mental retardation, cataracts, testicular atrophy, myotonia, and muscular dystrophy of adolescent onset (III-3). Case IV-7 could be considered to have neonatal MD although neonatal hypotonia and feeding and respiratory difficulties were denied. Case IV-5 appears to have NF alone, although the appearance of MD in this boy could conceivably be delayed for decades.

Secretor status and HLA haplotypes, assuming no recombination between the A and B loci, are given in the figure. All subjects were Lutheran a- b+. The inheritance of MD and secretor alleles is consistent with the MD locus in this family, as in other families, being linked to the secretor locus.¹¹ The limited data from this one family rule out very close linkage between the MD or NF loci and the HLA loci.

Discussion

Since both NF and MD were observed in all adults affected with either disorder who were examined, the possibility exists that a new disorder, with features of both illnesses, has been observed. This seems unlikely for three reasons. Firstly, the clinical features of both NF and MD in this family are quite typical for each of these conditions seen independently. The NF is of the peripheral type characterised by skeletal deformities and cutaneous abnormalities. Myotonic dystrophy in generation II is characterised by late adult onset, muscular dystrophy, and cataracts with little myotonia. In generation III, the MD is of young adult and adolescent onset with some retarded subjects and a significant amount of myotonia. The affected subject in generation IV has infantile onset of symptoms. As in this case, the mother is the affected parent in almost all instances of neonatal myotonia.¹² The fact that the inheritance of secretor alleles in this family is consistent with the well established close linkage between the secretor locus and MD locus¹¹ provides independent genetic evidence favouring identity between the locus for MD in this family and other families. Thirdly, it appears unlikely that the quite different features of NF and MD could result from the pleiotrophic effects of a single mutant gene.

The coincidence of two genetic disorders in affected subjects within a kindred can be produced by close linkage between the loci for the disorders, if the two disease alleles are in coupling. Thus, the phenotypic status of subjects I-1 and I-2 is critical. The information available suggests that I-1 had NF, but the origin of the MD is less clear. The description of temporalis muscle wasting and unsmiling face in I-1 provides suggestive evidence for MD in this woman. A history of cataracts and slurred speech in a nephew and cataracts in a niece of I-2, as well as a history of cataract in I-2 himself, provides weaker evidence for MD on his side of the family. Unfortunately, we have been unable to obtain any better estimate of the probability of MD in these subjects. Although a firm diagnosis of MD cannot be made in II-4, a description by family members of an unsmiling face and a flapping weakness of his hands provides a hint that he may have had MD. This subject and his brother II-3, who died at the age of 4, have been omitted from the linkage analysis. Generation IV is too young to be included in the analysis, since the clinical signs of either MD or NF could occur later in life. It is also possible that unaffected subjects in generation III could subsequently develop MD. Subjects III-2, aged 28, and III-10 aged 29, have passed through most of the age of risk.^{10 13} They are included in the analysis. III-9, aged 19, is excluded.

If the MD gene in generation II should originate from I-1, then there are no recombinants among the nine counted descendants in generations II and III. The lod score¹⁴ at a recombination frequency of 0 is 2.4. Should II-4 have both the MD and NF alleles and III-9 have neither, the lod score becomes 3.0. A score of 3.0 or greater is customarily accepted as a minimum requirement to establish linkage. On the other hand, if the MD gene in generation II should originate in I-2, then the segregation in this pedigree is strongly against linkage between MD and NF.

Only two single instances of the coincidental occurrence of NF and MD have been previously reported.^{6 7} We are unaware of any other study concerning linkage of these two disorders. The data in the family described here do not establish linkage between the loci for NF and MD. However, they are suggestive enough to prompt a search for similar informative families. More importantly, testing NF families for linkage to the secretor or Lutheran loci, both of which are linked to the locus for MD, offers the possibility for confirming or refuting the possibility of close linkage between the MD and NF loci.

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