Myotonic dystrophy and hyperparathyroidism: association with neurofibromatosis and multiple endocrine adenomatisos type 2A

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SUMMARY Four patients with hyperparathyroidism associated with myotonic dystrophy have been identified. All were females aged between 2 and 45 years. They were from three separate families, with two related patients being mother and daughter. In addition, one patient had medullary carcinoma of the thyroid and was diagnosed as having multiple endocrine adenomatisos, type 2A; another had an unspecified thyroid carcinoma; a third patient had neurofibromatosis. Our data suggest that myotonic dystrophy may somehow be associated with one or more of these disorders of neural crest origin.

Myotonic dystrophy is a disorder which affects many organ systems other than skeletal muscle. The endocrine system is commonly involved, but except for the rare occurrence of hyperthyroidism, it is typically associated with endocrine hypofunction. Since myotonic dystrophy is a relatively common autosomal dominant disorder, its occasional association with other disorders, both inherited and not inherited, would not be unexpected. In the course of several months, without a systematic search, we identified four patients with both myotonic dystrophy and hyperparathyroidism. In addition, all four patients had an additional disorder considered to be of neural crest origin, neurofibromatosis. We report the clinical features of three of these patients and their pedigrees and speculate whether myotonic dystrophy itself may be a neurofibromatosis in view of its association with these other disorders of tissues of neural crest origin.

Case reports

Case 1. A 44 year old woman was evaluated because of increasing muscle weakness. She had prior diagnoses of myotonic dystrophy and neurofibromatosis. At least seven other family members were also found to have neurofibromatosis, most of whom also had myotonic dystrophy (fig a). Physical examination revealed multiple cafe-au-lait spots of various sizes, mild hand weakness and grip and perception myotonia. Laboratory examinations revealed marked hypercalcaemia and elevation of the serum parathormone level. There was no evidence of parathyroid adenoma. Case 2. A 12 year old girl, product of a 39 week gestation pregnancy, was born cyanotic and hypotonic. After birth and a prolonged hospital stay, during which she developed multiple medical problems, she was diagnosed as having a spastic diplegia and mild mental retardation. The aetiology of her neurologic disorder was not clear, and the diagnosis of myotonic dystrophy was not suggested until age 9 years, although no diagnostic studies were performed at that time. She underwent multiple orthopaedic procedures over the years and at age 10 years, a muscle biopsy was performed to evaluate her hypotonia. The biopsy specimen was considered nondiagnostic and she continued to have slowly progressive muscle weakness, frequent falling and marked difficulty arising from chairs. She was first noted to have percussion myotonia at age 11 years. At age 12, she developed pneumonia and respiratory failure. Additional evaluation at that time included an EMG which revealed numerous myotonic discharges and she was diagnosed as having myotonic dystrophy. She was also found to have primary hyperparathyroidism, medullary carcinoma of the thyroid, and was diagnosed as having multiple endocrine adenomatosis type 2A. Following surgery for biopsy of thyroid and parathyroids she developed respiratory distress and died...
Myotonic dystrophy, hyperparathyroidism with neurofibromatosis and multiple endocrine adenomatosis

Myotonic dystrophy, hyperparathyroidism, and hyperparathyroidism, an association which we have failed to find on review of the medical literature. The four affected individuals were from three families with classical myotonic dystrophy, and hyperparathyroidism in other members, eliminating the possibility that the myotonia was due to a different type of disorder. Hyperparathyroidism was identified either because of complaints of increasing weakness (Cases 1 and 3) or because other considerations (presence of medullary carcinoma of the thyroid) led us to search for it (Case 2). All of the patients had elevated levels of parathormone demonstrated by radioimmunoassay. Hyperparathyroidism was apparently caused by parathyroid hyperplasia rather than by the presence of an adenoma in at least one of the patients (Case 1).

The increasing muscle weakness which preceded the diagnosis of hyperparathyroidism and its subsequent improvement after treatment in Cases 1 and 3 is not unexpected since the neuromuscular complications of hyperparathyroidism and hypercalcaemia are well known.2

Hyperparathyroidism is generally a sporadic disorder, although both autosomal dominant and recessive
inheritance are reported.3 Sipple's syndrome, MEA type 2A, seen in our Case 2, and presumably occurring in her mother, is inherited as an autosomal dominant trait, in which hyperparathyroidism, medullary carcinoma of the thyroid, and pheochromocytoma occur with high frequency.4 Recent linkage studies of MEA type 2A to segregation markers have been inconclusive,6 and as yet no linkage studies of familial hyperparathyroidism have been reported.

Linkage analysis studies in myotonic dystrophy have established that the myotonic dystrophy locus lies in the linkage group on chromosome 19 containing loci for the Lutheran blood group, the ABH secretor system, C3 complement component, peptidase D, and the apolipoproteins C2 and E.7 In our first family (fig a) both myotonic dystrophy and neurofibromatosis occurred together. Although this association has been reported once previously,8 prior studies of classical genetic markers in families with neurofibromatosis as well as a recent study using three chromosome 19 markers known to be linked to myotonic dystrophy,10 have failed to identify linkage. More important, a recent linkage analysis study of 128 individuals in 15 families in Utah has identified a region near the centromere of chromosome 17 as the location for the genetic defect(s) in neurofibromatosis.11 In family A, the chance association of the two genes on chromosomes 17 and 19 occurring in each of the offspring of 1:1 is 1:4 for each individual. The possibility that seven individuals would all inherit the same two random traits by chance alone is less than 1 × 106. This raises the possibility that family A represents a distinct genetic disorder with features of both myotonic dystrophy and neurofibromatosis, rather than the coincidental association of the two diseases. Regrettably, our cases were identified before the advent of current DNA technology which would have allowed for comparison of DNA marker studies of these cases with other families with myotonic dystrophy and neurofibromatosis.

Neurofibromatosis, an autosomal dominant disorder, has the major defining clinical features of multiple cafe-au-lait spots and multiple cutaneous fibromas.12 There are also a number of well recognised complications and variations of this disorder and varying degrees of severity. Neurofibromatosis is the most clinically important of the complex neurocristopathies, a group of disorders which are pathogenetically united by their origin in neural crest maldevelopment.13 Medullary carcinoma of the thyroid and the MEA syndromes are also neurocristopathies. Our data suggest that myotonic dystrophy may be linked to one or more of these disorders of tissues of neural crest origin.

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