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A patient with neurofibromatosis type 1 and myotonic dystrophy type 1

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Abstract

The association of two neurological disorders in one patient can result in diagnostic delay despite the presence of well known clinical features. We present here a patient with neurofibromatosis type 1 and concurrent myotonic dystrophy type 1, the latter diagnosed five years after its initial symptoms. The clinical features and the inheritance pattern common to both diseases are reviewed. Although both are autosomal dominant, the influence of genomic imprinting and parental lineage on their transmission and phenotype can differ. Appropriate genetic counseling is crucial in disorders affecting fertility like myotonic dystrophy type 1, and depends on early diagnosis. Awareness of such a diagnostic combination allow for early diagnosis and prevent delays in proper clinical management.

Keywords: Neurofibromatosis type 1, myotonic dystrophy, concurrent, association

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disease diagnosed by the presence of two of the five major criteria: hyperpigmented spots, freckles, optic nerve glioma, bone dysplasia, or NF1 in a first degree relative. The *NF1* gene on chromosome 17 is a large gene where spontaneous mutations are frequent; therefore, sporadic and familial NF1 cases are observed at equal rates.

Myotonic dystrophy type 1 (MD1) is another autosomal dominant condition. It results from an increased number of trinucleotide repeats in the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q13.3.[1] We present a rare patient with both diseases and discuss the clinical significance of this association.

CASE REPORT

This was a 45 year old woman who presented with weakness in all extremities, difficulty walking, and dizziness since 5 years ago. Past medical history included the diagnosis of NF1 based on hyperpigmented spots since birth, mild developmental delay in childhood, and neurofibromas since age 26 years. On examination, café-au-lait spots, axillary and inguinal freckling, dermal neurofibromas, cataract and reduced vision in the left eye were noted. Neurological examination revealed mild mental retardation, hypophonia, dysarthria, motor strength reduced to 3/5 in proximal upper extremities and 4/5 in foot dorsiflexors. Deep tendon reflexes were hypoactive. No pathological reflex or sensory deficit were elicited. Based on the diagnosis of NF1, MRI studies had been performed repeatedly for any intracranial or spinal tumors to explain her motor symptoms. When the patient was referred to our hospital, a more detailed family history revealed her parents were first cousins, her brother had died of a heart disorder at age 40, and two cousins reportedly had weakness and walking difficulty without any specific diagnosis. On examination, atrophy in temporal muscles, cutaneous neurofibromas (Figure 1 a,b), myotonia in thenar muscles and tongue were observed (Figure 2 a,b) in addition to the findings described above. Electromyography demonstrated myotonic discharges and rare low-voltage myogenic motor unit potentials. Echocardiography was normal. Genetic analysis showed an increased number of CTG trinucleotide repeats (n=120, normal range: 5-37) in the 3' non-translated region of the *DMPK* gene, confirming the diagnosis of MD1.

DISCUSSION

The prevalence of NF1 is 1/3500 and of MD1 is

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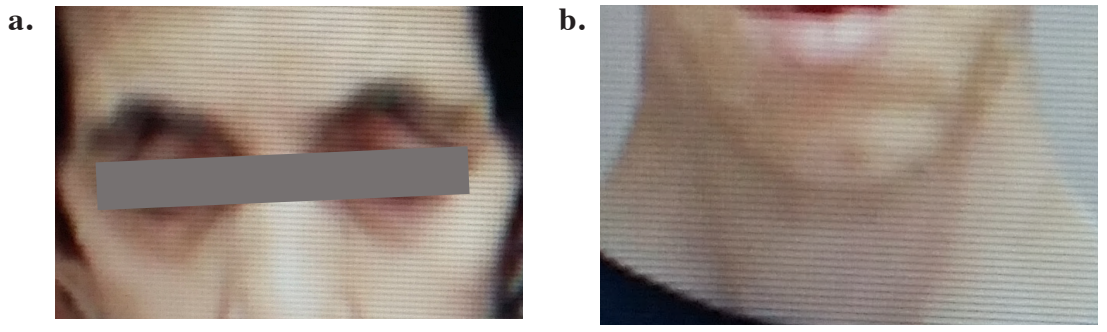

Figure 1. a) Atrophy of temporal muscles. b) Cutaneous neurofibromas over the chin.

3-15/100000: therefore coincidental association of these two disorders is possible but rare, as has been covered in a few reports including a family with seven members affected by both disorders over four generations.[2-8] The pre-existing diagnosis of NF1 in our patient had precluded the diagnosis of MD1 during several years of follow-up. Investigations including numerous cranial and spinal MR examinations had produced unremarkable results. In MD1, brain MRI may be normal or show nonspecific findings such as cerebral atrophy and hyperintense white matter lesions.[9] The physical and neurological findings of MD1 can be masked by or attributed to those of NF1. The features common to both disorders are listed in the Table 1.

Our patient's main complaint was weakness, leading to investigations for peripheral neuropathy or spinal tumors expected in NF1. The peripheral neuropathy of NF1 can occur even in the absence of neurofibromas on peripheral nerves; therefore its pathogenesis is unclear.[14] Hereditary neuropathies have also been reported in NF1 patients.[17] Parental consanguinity in the patient's family raised the possibility of a recessive hereditary neuropathy. However the likelihood of another neurological condition had not been considered in this patient. In particular, myotonia had not been looked for, probably due to the influence of the more obvious diagnosis, NF1.

Comorbid conditions can potentiate each other's effect on quality of life. Both NF1 and MD1 are multisystemic disorders causing chronic neurological and extra-neurological problems: population studies show mental difficulties, chronic lung disease, epilepsy in NF1 patients and depression, cardiomyopathy and diabetes mellitus in MD1 patients are more frequent compared to

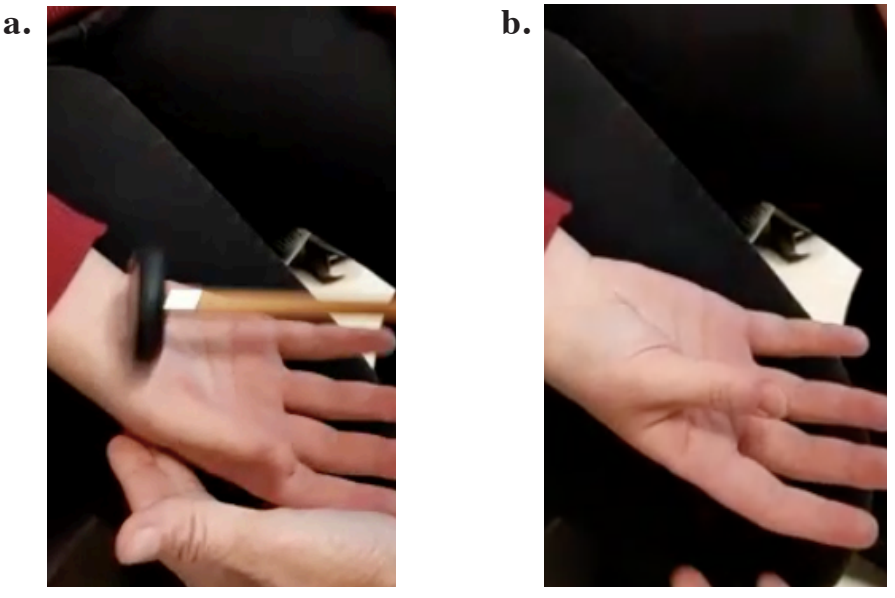

Figure 2. a) Myotonic reaction to percussion in thenar muscle. b) Slow relaxation over 4 seconds.

Table 1: Systems involved in both myotonic dystrophy type 1 and neurofibromatosis type 1.

System	Myotonic dystrophy type 1	Neurofibromatosis type 1
Craniofacial	Temporal atrophy Elongated face Wider head, shorter head length Mid-facial hypoplasia[10]	Macrocephaly Sphenoid dysplasia
Skin	Pilomatrixoma Basal cell carcinoma Multiple hyperpigmented nevi[11]	Dermal and subdermal neurofibromas Multiple hyperpigmented macules
Cancer risk	Various cancers[12]	Nervous system tumors
Neurological	Cognitive deterioration Motor weakness Peripheral neuropathy, usually subclinical pain[15]	Mild cognitive and attention deficit Hypotonia, muscle weakness[13] Peripheral neuropathy[14] Pain[16]
Inheritance	AD, transmission differs between maternal and paternal lineage, imprinting	AD, maternal deletions more transmissible, no change over generations

AD: autosomal dominant.

control populations.[18,19] The quality of life, mood and affect of our patient were markedly impaired and required specific treatment.

Besides the clinical interference between co-existing diseases, interaction is also possible in their intracellular pathways. NF1 is a RASopathy where the Ras/Raf-1/MEK/ERK axis is dysregulated. Because Ras pathway members Rac-1 and Raf-1 stimulate *DMPK* activity, overactivity of Ras in NF1 might modulate the phenotype of MD1.[20] In our patient, the clinical features of MD1 were milder than her affected siblings; nevertheless, phenotypic modification of MD1 by NF1 can not be ascertained because the phenotype associated with intermediate-size expansions of CTG repeats is highly variable.

Genetic counseling constitutes another important aspect of the management of such patients. Although both NF1 and MD1 are autosomal dominant diseases, their inheritance pattern carry particular features. In NF1 parental lineage may influence the phenotype.[21] In MD1, the main factor affecting the severity and transmission is the length of trinucleotide repeat expansion, but maternal inheritance may also play a role in a more severe phenotype and genomic imprinting in the sibling.[22,23] This complicates genetic counseling in such families. Moreover, fertility is reduced in MD1 and these patients are likely to resort to assisted reproduction techniques. Therefore discussion of preimplantation genetic diagnosis based on early and accurate diagnosis of the disease is warranted.

This case exemplifies difficulties in the diagnosis of coexistent neurological diseases. Each disorder can potentiate the other's symptoms and effect on the quality of life of the patient. The significance of this case for the clinician lies particularly in awareness of overlapping symptoms and signs altering or masking a phenotype. A complete examination and exclusion of other conditions is warranted in all patients, even those with a pre-existing or obvious diagnosis.

DISCLOSURE

Ethics: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Conflict of interest: None.

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