Background: Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), can present with parkinsonism. However, classically, atypical features, including pyramidal and cerebellar signs, peripheral neuropathy, and/or anterior horn cell dysfunction, are also seen. Levodopa responsiveness is unusual in this disorder.

Objective: To determine the cause of apparent parkinsonism suggestive of Parkinson disease (PD) in a large family of African origin.

Methods: We studied a large family in which apparent autosomal dominant parkinsonism suggestive of PD occurs in order to find the causal genetic mutation. Affected and unaffected family members were screened for the presence of a pathogenic expansion at the MJD/SCA3 locus using a polymerase chain reaction polyacrylamide gel electrophoresis–based assay.

Results: Three of the 4 individuals who were examined have a phenotype reminiscent of PD. Specifically, they have at least 2 of the cardinal features, are levodopa responsive, and have no atypical features. All affected family members were shown to possess pathogenic expansions in the MJD/SCA3 gene.

Conclusions: Parkinsonism suggestive of PD due to MJD/SCA3 has not been previously reported, to our knowledge. However, atypical, though also levodopa-responsive, parkinsonism has been previously reported to occur in African American families, suggesting that this phenotype is associated with African ancestry. In this regard, it is perhaps significant that all the individuals with parkinsonism have relatively low numbers of repeats (normal, 16-34; pathologic, 60-84). In families in which linkage analysis is being performed to determine a locus for autosomal dominant parkinsonism suggestive of PD, evaluation for the MJD/SCA3 mutation is indicated.

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The family tree, along with the number of repeats at the SCA3 locus, is shown in the Figure. A summary of the clinical characteristics and repeat length is presented in the Table. The clinical characteristics of those individuals who were examined by one or more of us are presented in detail below.

Proband (2001, Coriell Cell Repositories No. GM 15904)

A previously well 36-year-old woman noted the insidious onset and gradual progression of motor slowing for 5 years. Her...
METHODS

Genomic DNA was isolated from whole blood using genomic DNA purification kits (Wizard). Polymerase chain reaction amplification was performed in a 25-µL reaction containing 25 ng of genomic DNA, 10 pmol of both forward and reverse oligonucleotide custom primers (F 5’-CCAGTGACTATTTGATTCG-3’, 5’ labeled with Tet; R 5’-TGCCCTTCTCATGCGATGAA-3’, Life Technologies, Rockville, Md), 1× manufacturer’s buffer, 1× Q solution (Qiagen Inc, Valencia, Calif), 200-µmol/L deoxynucleotide triphosphates (Amersham Pharmacia Biotech Inc, Piscataway, NJ), and 0.2 U of Taq DNA polymerase (Qiagen Inc). Polymerase chain reaction was run on a commercially available machine (Touchdown; Hybaid, Franklin, Mass) using the following conditions: 5 minutes of denaturation at 95°C, followed by 35 cycles at 95°C for 30 seconds, 55°C for 20 seconds, and 72°C for 30 seconds, and then by a final 10-minute incubation at 72°C. Five microliters of each reaction was run on a 2% agarose gel to confirm amplification and to exclude the possibility of pathogenic extensions beyond the ladder size (300 base pairs [bp]) used on the automated sequencer. One microliter of the polymerase chain reaction product at a dilution of 1:50 was electrophoresed on a 6% polyacrylamide gel containing 25 ng of genomic DNA, 10 pmol of both forward and reverse oligonucleotide custom primers (ABI377 96XL; Applied Biosystems, Foster City, Calif), and 0.2 U of Taq DNA polymerase (Qiagen Inc). Sizing was performed using a 50- to 500-bp tetramethylrhodamine ladder (TAMRA; Applied Biosystems) according to the manufacturer’s instructions. Also, to confirm that extensions were uninterrupted repeats, polymerase chain reaction was performed on each case using exactly the same conditions as mentioned earlier but using an unlabeled forward primer. The resulting products were then sequenced with these primers and a reaction kit (BigDye Terminator Ready Reaction Kit; Applied Biosystems) and analyzed using an automated sequencer (ABI377 96XL; Applied Biosystems) according to the manufacturer’s instructions.

The 65-year-old half-uncle of the proband developed Parkinsonism at 57 years of age characterized by a resting tremor of his left upper extremity, mild bradykinesia, and a reduced arm swing. Throughout the course of his illness, his major complaint has been a coarse, predominantly left-sided tremor that affected both upper and lower extremities. He has been receiving levodopa replacement therapy for 7 years, with good effect, but over the last year, he has developed levodopa-related motor fluctuations without dyskinesias. At the time of examination, he was taking 900 mg/d of levodopa (Madopar).
On examination in the “on” state, his mental status was normal. His cranial nerves were normal except for slowed saccades. His eye movements were full. He had moderate masked facies and moderate hypophonia. There was intermittent resting tremor in all 4 extremities, more marked on the left side of his body. His posture was slightly stooped, with absence of a postural response on pull testing. His gait was slightly hesitant, with a reduced arm swing. There was a mild degree of bradykinesia, with no rigidity. Strength, sensation, and deep tendon reflexes were normal.

A 51-year-old woman has had difficulty with back pain and stiffness since her teens. These symptoms have been attributed to scoliosis and have not been formally evaluated or treated. She has noted in the past 10 to 12 months that her left foot involuntarily turns inward, especially first thing in the morning. This is only moderately bothersome to her, and she has not sought the help of a physician.

The findings of her mental status examination were normal. Her cranial nerve examination was significant for saccadic pursuits. Scoliosis was apparent during the gait examination. She had left foot dystonia while in re-pose, which worsened slightly when she was ambulating. The results of the rest of the neurological examination were normal.

Parkinsonian features have been previously reported as the predominant phenotype of the MJD/SCA3 mutation (MJD type 4), usually accompanied by robust atypical features. However, 3 of the 4 individuals from the pedigree described herein have a phenotype suggestive of PD. Specifically, they have at least 2 of the cardinal features, are levodopa responsive, and have no atypical features. Although more extensive testing (eg, electromyography with nerve conduction studies) might be revealing, this was done in 1 of the 4 individuals, and the results were normal. Furthermore, we suspect that if these patients walked into the standard neurology practice today, they would be diagnosed as having PD. While there has been no neuropathologic examination to date in this kindred, we would expect it to be unlikely that they would
have Lewy body disease. To our knowledge, the remarkable combination of symptoms in MJD/SCA3 that were found in our kindred has not been previously documented, although it is of interest that an atypical, though also levodopa-responsive, parkinsonism has been previously reported to occur in African American families. Thus, the parkinsonian phenotype encompassing both “typical” (this work) and “atypical” (see reference 5) features may be associated with African ancestry, although this theory clearly will require further investigation in more families of diverse ethnic origin before a secure conclusion can be reached. In this regard, it is perhaps significant that all the individuals with parkinsonism have relatively low numbers of repeats (normal, 16-34; pathologic, 60-84), although this is likely not the only factor.

These observations are of importance for 3 reasons. First, MJD/SCA3 should particularly be considered in the differential diagnosis of parkinsonism that is suggestive of PD in blacks. Second, our findings may imply the possibility of genetic modifiers, which influence the phenotype of the mutant allele in different racial groups. Finally, these results emphasize that in other studies in which familial parkinsonism is being studied, care should be exercised in identifying individuals in which the mutations is at the MJD/SCA3 locus. In those families in which linkage analysis is being performed to determine a locus for autosomal dominant parkinsonism that is suggestive of PD, evaluation for the MJD/SCA3 mutation is particularly important.

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REFERENCES