Heterogeneity of Presentation and Outcome in the Irish Rapid-Onset Dystonia–Parkinsonism Kindred

Andrew McKeon, MB, MRCPI,[1]
Laurie J. Ozelius, MD,[2] Oria Hardiman, MD, PRCPI,[1]
Matthew J. Greenway, MB,[1] and
Sean J. Pittock, MD[1,3]*

[1]*Department of Neurology, Beaumont Hospital Dublin and Royal College of Surgeons in Ireland, Dublin, Ireland*
[2]*Department of Molecular Genetics, Albert Einstein College of Medicine, Bronx, New York, USA* [3]*Departments of Neurology and Laboratory Medicine & Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA*

Video 

Abstract: **The authors report a 7-year follow-up video study and molecular data on the Irish rapid-onset dystonia–Parkinsonism kindred. All affected patients tested had a missense mutation in the Na^+/K^+ -ATPase α3 subunit (ATP1A3), twice previously identified, suggestive of a mutation hotspot. Clinical presentation, progression, and outcome in this kindred is varied. Some patients remain stable over many years, others worsen, have a fluctuating course, or improve over time. To date there have been no effective treatments for this disorder, although Na^+/K^+ ATPase may be a future therapeutic target. The broad phenotypic spectrum of RDP described in the text and detailed in the video, should be considered when evaluating patients with dystonia.** © 2007 Movement Disorder Society

Key words: rapid-onset dystonia-Parkinsonism; Irish kindred; ATP1A3 mutation

Disease description

Rapid-onset dystonia–Parkinsonism (RDP, DYT12), is a rare autosomal dominant movement disorder, characterized by the abrupt onset of orofacial, bulbar, and limb dystonia with predominant upper limb involvement, a stable course, and a lack of levodopa response. Other findings include psychiatric comorbidity, onset during a stressful event, and a suggestion of incomplete penetrance and anticipation. The RDP gene was mapped to an 8 cM region on chromosome 19q13 in two RDP families[1] and was subsequently confirmed in the Irish kindred.[2] More recently, six different mutations in the Na^+/K^+-ATPase α3 (ATP1A3) gene have been elucidated in RDP.[3] There is a paucity of video and longitudinal data on this disorder in the literature. We report a 7-year follow-up study and molecular data on the Irish kindred.

Pathogenesis

Reason for study

PATIENTS AND METHODS

We interviewed and examined 11 surviving members of the Irish RDP kindred, and videotaped all those who had features of RDP. In each case, notes and video material available from 1998 were reviewed. Blood samples were obtained from all but 1 (Patient III:1) of those with features of RDP. To detect mutations in the ATP1A3 gene, all 23 exons were amplified using previously published techniques.[3] A revised pedigree was drawn from the results. Written informed consent was obtained before blood draw and videotaping. This study was approved by the Beaumont Hospital Institutional Review Board.

Interview vs chart

Information gathered

REB

RESULTS

Nine affected patients were identified (Fig. 1, see Video, Segment 1), two of whom (Patients II:7 and III:5) are new cases. All 8 of those tested had a C1838T mutation and codon change T613M in exon 14 of the ATP1A3 gene (Fig. 1).

Patient I:1

This 84-year-old man, initially diagnosed with stroke, has right upper limb and foot dystonia with bradykinesia since his 50s. No deterioration has been noted over the follow-up period.

Patient II:3

This 50-year-old father of III:3 and III:5 had onset of focal symptoms on the left side in his 40s. He has a low level of disability and has demonstrated no progression.

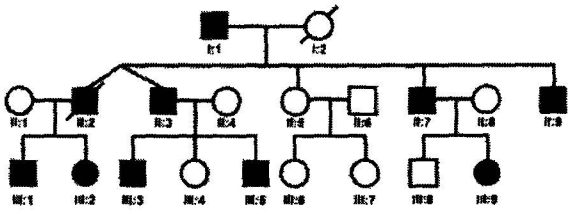

FIG. 1. The Irish rapid-onset dystonia–Parkinsonism (RDP) pedigree shows 10 affected individuals, 8 of whom were tested for ATP1A3 mutations. Patient II:2 is deceased, and Patient III:1 did not consent to testing. All those tested had a C1838T mutation and codon change T613M in exon 14 of the ATP1A3 gene. Of note, Patient III:5 was incorrectly illustrated as female in Pittock and associates, 2000.[2]

This article includes Supplementary Video, available online at http://www.interscience.wiley.com/jpages/0885-3185/suppmat

*Correspondence to: Dr. Sean J. Pittock, Department of Neurology, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905.
E-mail: pittock.sean@mayo.edu

Received 20 September 2006; accepted 17 October 2006.
Published online 21 May 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21335

The video demonstrates his abnormal gait and left sided dystonia and bradykinesia.

Patient II:7

The 47-year-old father of III:9 was an obligate carrier in 1998, and presented in 2005 with poor grip in his right upper limb that initially evolved and then stabilized over 1 year. He has reduced arm swing and foot dragging on the right, with low amplitude movements and dystonia of his right hand.

Patient II:9

At baseline, this 45-year-old man has mild dysarthria and Parkinsonism affecting his left upper limb. While there has been no progression in his illness, he complains of intermittent episodes of uncontrollable left upper limb posturing and spasm under conditions of psychological stress. As described previously, he has developed a social phobia resulting from embarrassment related to these episodes. In the video, the patient becomes acutely embarrassed and his dystonia worsens when another doctor enters the room.

Patient III:1

This 24-year-old brother of the proband, with a history of learning disability and generalized epilepsy, developed both left upper and lower limb dystonia, which evolved over 6 weeks when he was 17 years of age. His mother has juvenile myoclonic epilepsy. His father, previously described, had a generalized dystonia and died at age 33 from aspiration pneumonia[2] Overall, there has been no functional change in Patient III:1. He mobilizes by hopping on his right leg with the left foot held in plantar flexion and inversion.

Patient III:2

The Irish proband, now 21 years old, described by Webb and colleagues in 1999,[4] developed severe disability secondary to the acute onset of bulbar and limb dystonia at 14 years of age. There has been no change in her functional status. She tolerates normal oral diet, and her verbal communication is minimal. She requires large doses of oral baclofen and diazepam to control painful spasms. She has developed a scoliosis and required surgical release of her left biceps tendon to treat severe flexor spasm. The video demonstrates her taking a few steps with assistance of two, using the sensory trick of biting on a towel.

Patient III:3

This 24-year-old man has exhibited significant progression in his illness over the 7 years since diagnosis. He originally presented with acute onset of dysarthria, orofacial dystonia, and bilateral limb dystonia, which occurred during a stressful event. Since then, his gait has deteriorated, he is rollator dependent, and drags both feet in a plantar-flexed and inverted posture. In addition, his bulbar dystonia has deteriorated and he temporarily required gastrostomy feeding to maintain nutrition. A painful flexion contracture of the fingers of his left hand is treated with regular injections of botulinum toxin. Depression was an early feature of his illness and responded to sertraline.

Patient III:5

The 22-year-old brother of Patient III:3 noted clumsiness of right hand movements and a tendency to slur his words and drag his right foot when fatigued 1 year ago. His examination revealed mild rigidity of right upper and lower limbs, with dystonia affecting right hand function but no objective bulbar features.

Patient III:9

This 17-year-old woman had acute onset of generalized dystonia with upper limb and bulbar predominance at age 8, after a fall in a school yard. She initially had demonstrated progression over 2 months and then improvement in voice production over 1 year. Over the past 7 years, her mobility has improved, although she has had no further improvement in bulbar and upper limb function. She also had a depressive episode after the onset of her illness, which responded well to psychotherapy.

Examination reveals a sardonic smile, mild orofacial dystonia, and bradykinesia of facial expression. She has bulbar dystonia with strangled sounding speech. She has dystonic posturing of both upper limbs, exacerbated on asking her to run. Rapid, fine movements were mildly reduced in both upper limbs.

DISCUSSION

The C1838T mutation and codon change T613M in exon 14 of the ATP1A3 gene has been identified twice previously in RDP; once in a Polish family with 4 affected members, and once in a sporadic case, suggesting a mutation hotspot.[3,5,6] However, there seems to be no phenotype specific to this mutation, with patients in both Irish and Polish families having a wide range of presentations, suggesting that environmental or other genetic factors are influencing expression. Previous descriptions of "typical" or classic[7] RDP allude to stabilization within 4 weeks and more prominent upper limb involvement. However, many patients have a mild focal dystonia alone, others may have severe lower limb involvement, and others again may have a slowly progressive course.[8,9] Three members of the Irish kindred demonstrate severe lower limb involvement (Patients III:1,

III:2, III:3), 1 of whom (III:3) has had a slowly progressive course over 7 years. On the other hand, 4 of the patients described (Patients I:1, II:3, II:7, III:5) had focal onset of mild dystonia and Parkinsonism with no progression and 2 patients, although severely affected, have not progressed (III:2, III:9).

Although psychiatric comorbidity in this family includes anxiety, panic, and social phobia,[2] major depressive episodes have only been seen in 2 patients (Patients III:3, III:9). These episodes occurred at the onset of severe disability and responded well to treatment, with both patients remaining in remission since. Although there is a maternal family history of epilepsy in relation to Patient III:1, given that mutations in neuron ion channels have been identified in some epilepsy syndromes, we cannot exclude the possibility that seizures are part of this patient's RDP phenotype. Although possible nonpenetrance has been previously described,[2,5,7,8] in the case of the Irish kindred, Patient II:7 simply presented later than his daughter (Patient III:9).

One family member in particular (Patient II:9) has marked fluctuations, having a mild segmental dystonia at baseline, which can be severely exacerbated at times of psychological stress. A mutation in a Na^+/K^+-ATPase supports the possibility of a fluctuating course in RDP, although it is unclear why most patients seem to develop a fixed dystonia and Patient II:9 can somehow compensate and return to baseline.

Voltage-gated sodium channels are essential for the initiation and propagation of action potentials in neurons. The transmembrane sodium gradient is subsequently restored by the activity of the ATP-dependent sodium/potassium pump. The Na^+/K^+-ATPase $\alpha 3$ subunit, present in both human brain and heart tissue, is thought to be important in restoring resting membrane potential in neurons. A recent study of mutations similar to those in RDP induced in the $\alpha 1$-isoform of rat kidney Na^+/K^+-ATPase demonstrated reduced binding of sodium to a dysfunctional Na^+/K^+-ATPase on the cytosolic side of the membrane.[10] In the case of a T618M mutation (similar to the mutation in this family), this reduced binding may be caused by an enhanced ability of potassium to compete with sodium for binding sites.

Given the increasing amount of literature of both familial and sporadic RDP cases,[6,11,12] the broader phenotypic spectrum of RDP as described in this study should be considered in the differential diagnosis when assessing patients with dystonia. Although, the treatment of RDP has remained unsatisfactory[2,11] the fluctuations and improvements in the natural course of this disorder support the concept of reversibility in RDP and hold promise for future therapeutic benefit.

Acknowledgments: We thank Dr. Mary King, Dr. Raymond Murphy, and Dr. David Webb for access to patients and records for this study; Professor Andrew Greene for storing all blood samples; and the individual patients for taking part in the study.

LEGEND TO THE VIDEO

The video contains the key clinical features of the individual members of the Irish RDP kindred. See text of manuscript for detail.

REFERENCES

1. Kramer PL, Mineta M, Klein C, et al. Rapid-onset dystonia-parkinsonism: linkage to chromosome 19q13. Ann Neurol 1999; 46:176–182.
2. Pittock SJ, Joyce C, O'Keane V, et al. Rapid-onset dystonia-parkinsonism: a clinical and genetic analysis of a new kindred. Neurology 2000;55:991–995.
3. de Carvalho Aguiar P, Sweadner KJ, Penniston JT, et al. Mutations in the Na+/K+ -ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron 2004;43:169–175.
4. Webb DW, Broderick A, Brashear A, Dobyns WB. Rapid onset dystonia-parkinsonism in a 14-year-old girl. Eur J Paediatr Neurol 1999;3:171–173.
5. Zaremba J, Mierzewska H, Lysiak Z, Kramer P, Ozelius LJ, Brashear A. Rapid-onset dystonia-parkinsonism: a fourth family consistent with linkage to chromosome 19q13. Mov Disord 2004; 19:1506–1510.
6. Linazasoro G, Indakoetxea B, Ruiz J, Van Blercom N, Lasa A. Possible sporadic rapid-onset dystonia-parkinsonism. Mov Disord 2002;17:608–609.
7. Brashear A, DeLeon D, Bressman SB, Thyagarajan D, Farlow MR, Dobyns WB. Rapid-onset dystonia-parkinsonism in a second family. Neurology 1997;48:1066–1069.
8. Dobyns WB, Ozelius LJ, Kramer PL, et al. Rapid-onset dystonia-parkinsonism. Neurology 1993;43:2596–2602.
9. Brashear A, Farlow MR, Butler IJ, Kasarskis EJ, Dobyns WB. Variable phenotype of rapid-onset dystonia-parkinsonism. Mov Disord 1996;11:151–156.
10. Rodacker V, Toustrop-Jensen M, Vilsen B. Mutations Phe785Leu and Thr618Met in Na+,K+ -ATPase, associated with familial rapid-onset dystonia parkinsonism, interfere with Na+ interaction by distinct mechanisms. J Biol Chem 2006:281:18539–18548.
11. Deutschlander A, Asmus F, Gasser T, Steude U, Botzel K. Sporadic rapid-onset dystonia-parkinsonism syndrome: failure of bilateral pallidal stimulation. Mov Disord 2005;20:254–257.
12. Kamphuis DJ, Koelman H, Lees AJ, Tijssen MA. Sporadic rapid-onset dystonia-parkinsonism presenting as Parkinson's disease. Mov Disord 2005;21:118–119.