2. Prader A, Labhart A, Willi H: Ein syndrome von adipositas, Kleinwuchs, Kryptorchismus and Oligophreniech myatonieartigen Zustland in neugoborenanalter. Schweiz Med Wochenschr 1956; 86:1260-1261
3. Ledbetter DH, Riccardi VM, Airhart SD, et al: Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. N Engl J Med 1981; 304:325–329
4. Scheimann A: Prader-Willi syndrome. e-medicine
5. Cassidy SB: Prader-Willi syndrome. J Med Genet 1997; 34:917–923
6. Cassidy SB, Schwartz S: Prader-Willi and Angelman syndromes: disorders of genomic imprinting. Medicine 1998; 77:140–151
7. Butler M: Prader-Willi syndrome: current understanding of cause and diagnosis. Am J Med Genet 1990; 35:319–332
8. Kaplan HI, Sadock BJ: Prader-Willi syndrome, in Synopsis of Psychiatry, 8th ed. Baltimore, Lippincott Williams & Wilkins, 1998, p 1141
9. Dykens EM, Cassidy SB: Prader-Willi syndrome: genetic, behavioral, and treatment issues. Child Adol Psychiatr Clin N Am 1996; 5;913–927

Association of Familial Ataxia and Restless Legs Syndrome

SIR: Restless legs syndrome (RLS), characterized by an intense urge to move the lower extremities especially during the night, is associated with a number of medical conditions, such as uremia, iron deficiency, and neuropathy. RLS with a prevalence of 5% to 15%, is frequently underdiagnosed[1–3] and can be confused with anxiety states and other psychological syndromes, hyperthyroidism and drug-induced akathisia. Previous reports have highlighted an association between RLS and familial spinocerebellar ataxias (SCA) in German and Dutch patients.[2–5] However, the long-term association of these two conditions is unknown. The prevalence of RLS is much rarer among Asians,[6] and to our knowledge, RLS has not been reported in SCA patients in Asia.

Here, we report an Asian patient with SCA who presented with restless legs symptoms that were initially attributed to stress and anxiety. We examined the relationship between RLS and SCA symptoms in this patient over a few years to highlight the need to recognize their coexistence early since RLS could be effectively treated.

Case Report

The patient of Asian origin presented with progressive unsteady gait and frequent falls. He had signs of cerebellar dysfunction, generalized hyperreflexia and lower limb spasticity, and was confirmed to have autosomal dominant SCA type 3 (SCA3), with an abnormal *CAG* trinucleotide repeat expansion. One year after the onset of his ataxia, he complained of an urge to move his lower extremities, particularly when at rest. This was preceded by an abnormal sensation in his toes and feet, which at times extended to his knees, described as "crawling," "creeping," and "itching." He was troubled and anxious because the urge and sensation were often intense and distressing, and he had to move his legs and get up to walk to obtain relief. He was more aware of his symptoms during quiet time in the evening or night and when not distracted by other activities. He frequently woke up more than 10 times nightly because of sensation associated with restless legs and complained of poor sleep quality. His symptoms were initially attributed to his anxiety and depression and treatment for these symptoms was not effective. Subsequently, he was diagnosed with RLS based on the International Restless Legs Syndrome Study Group criteria.[5] After L-dopa was prescribed, his symptoms improved significantly. Investigations did not reveal a secondary cause for his RLS. Full blood count, urea/creatinine/electrolytes, and serum ferritin levels were normal. A nerve conduction test did not reveal any significant peripheral neuropathy. He was followed up over a 3-year period. His RLS symptoms appeared to progress with deterioration of his ataxia symptoms but could be controlled with L-dopa. His RLS symptoms would reemerge with withdrawal of the medication.

Comment

RLS was most likely related to the patient's ataxia condition as the patient did not have any past or family history of RLS, his symptoms came only after the onset of his ataxia, and the clinical severity of both diseases appeared to move in tandem over a long period of time. Investigations did not reveal any evidence of anemia, renal failure, peripheral neuropathy, or arthritis, conditions which may predispose to RLS symptoms.

Functional imaging studies have provided evidence implicating dopaminergic system impairment in RLS. Similarly, striato-nigral involvement has been demonstrated in neuropathological specimens of SCA3. Hence, it is possible that SCA3 and RLS may share a common pathophysiological mechanism. RLS and sensorimotor axonal neuropathy have been associated with intermediate *CAG* repeat size (53 and 54 repeats) in an SCA3 Dutch family.[5] Our RLS patient had an abnormal *CAG* repeat size (>60 repeats) and no neuropathy. Whether there is a correlation between the size of the *CAG* repeat expansion and the risk of RLS symptoms is not known.

RLS symptoms can be confused with stress and anxiety in patients with familial SCA. The long-term follow-up of our patient supports the association of RLS and SCA reported in Caucasian patients. We

need to recognize RLS early, even in Asian populations where RLS is apparently rare so that appropriate effective treatment can be instituted. Further studies into the pathophysiological link between RLS and SCA3 would be of academic interest.

ENG-KING TAN, M.D.
National Neuroscience Institute, SingHealth Research, Singapore

References

1. Walters AS: Toward a better definition of restless legs syndrome: The International Restless Legs Syndrome study group. Mov Disord 1995; 10:634–642
2. Tan EK, Ondo W: Restless legs syndrome: clinical features and treatment. Am J Med Sci 2000; 319:397–403
3. Abele M, Burk K, Laccone F, et al: Restless legs syndrome in spinocerebellar ataxia types 1, 2, and 3. J Neurol 2001; 248:311–314
4. Schols L, Haan J, Riess O, et al: Sleep disturbance in spinocerebellar ataxias: is the SCA3 mutation a cause of restless legs syndrome? Neurol 1998; 51:1603–1607
5. van Alfen N, Sinke RJ, Zwarts MJ, et al: Intermediate CAG repeat lengths (53,54) for MJD/SCA3 are associated with an abnormal phenotype. Ann Neurol 2001; 49:805–807
6. Tan EK, Seah A, See SJ, et al: Restless legs syndrome in an asian population: a study in Singapore. Mov Disord 2001; 16:577–579

Does Aripiprazole Have a Role in Treating Cognitive Impairment in Parkinson's Disease?

SIR: Case reports of aripiprazole treating psychosis in Parkinson's disease have been reported.[1] We present a case in which aripiprazole, an atypical antipsychotic with 5HT2A antagonist, 5HT1A partial agonist activity, improved cognitive functioning in a 57-year-old veteran with a recent diagnosis of Parkinson's disease and depression.[2]

Case Report

The patient had marked cognitive impairment confirmed by neuropsychiatric testing, indicating slowing in processing information (bradyphrenia), with learning and memory deficits. The patient presented to scheduled appointments along with a social worker because of difficulty in expressing himself. Medications comprised paxil, 20mg, and his antiparkinsons medications (sinemet and artane). He continued to do poorly in the subsequent months, with increasing episodes of confusion, depression, apathy, social isolation, and decline in working memory. Residential care was being considered. After several failed attempts in adjusting medications, the patient was started on a regimen of aripiprazole, 5 mg and increased to 15 mg, in the hopes of improving cognition. When the patient presented subsequently for his appointment, he showed marked signs of cognitive improvement. His memory, mood, verbal fluency, processing speed, alertness, and interaction dramatically improved. In the past, he was unable to drive a vehicle but since being on aripiprazole, he has been driving his vehicle with no further episodes of confusion. He continues to do well on aripiprazole.

Comment

Early cognitive impairment with five times the risk of developing dementia is noted in Parkinson's patients due to dopamine and cholinergic deficits in the prefrontal cortex[3,4] with frontal and hippocampal atrophy noted in imaging studies of nondemented Parkinson's patients.[3] Rivastigmine was shown to improve cognitive slowing in Parkinson's disease, suggesting acetylcholine is involved in processing information speed.[3] Aripiprazole partial agonist action on 5HT1A may increase cortical acetylcholine release, improving cognition.[5] Loss of pigmented neurons in the ventral tegmental area in a small group of patients with Parkinson's disease have been reported.[3] Systemic administration of the 5-HT2A receptor antagonist enhances activity of midbrain dopamine neurons, increasing dopamine in the prefrontal cortex.[6,7] 5HT1A and 5HT2A receptors are located primarily on the pyramidal cortical neurons (5HT2A receptors excitatory and 5HT1A receptors inhibitory), mediating a physiological balance between excitatory and inhibitory inputs onto prefrontal pyramidal neurons.[2] Aripiprazole's unique actions on D2 receptors possibily depend upon the cellular milieu of D2 receptors (receptor and G protein complement and concentration) eliciting agonist, antagonist, partial agonist activity,[2] which may enhance cognitive function. The most common psychiatric disturbance in Parkinson's disease is depression with a frequency of approximately 40%, occurring usually in the early and late stages of the disease.[4,8] A significant correlation exists between cognitive deficits and severity of depression.[4] Depression and dementia, not motor symptoms, were associated with increased mortality in Parkinson's disease.[2] Aripiprazole is a unique atypical which may have a role in improving mood and cognition in Parkinson's disease.

SARBJOT SINGH AJIT
University of Missouri, Columbia, Mo.

References

1. Lopez-Meza E, Ruiz-Chow A, Ramirez-Bermudez J: Aripiprazole in psychosis associated with Parkinsons disease. J Neuropsychiatry Clin Neurosci 2005;17:421–422