Commentary

Paroxysmal dyskinesias (PxDs) are characterized by recurrent attacks with involuntary movements in which abnormal movements are absent between the attacks. In 1995, Demirkiran and Jankovic[1] classified dyskinesia as based on precipitating events, duration of attacks, and etiology. If the attacks have a kinesigenic character which indicates that abnormal movements are induced by sudden body movements, the clinical picture is termed as 'paroxysmal kinesigenic dyskinesia' (PKD); otherwise, the term 'paroxysmal nonkinesigenic dyskinesia' (PNKD) is used. If the attacks are provoked by exercise, the picture is classified as 'paroxysmal exercise-induced dyskinesia' (PED). If the attacks mostly occur during non-REM (REM: Rapid eye movement) sleep, the category is 'paroxysmal hypnogenic dyskinesia' (PHD). This classification also divides PxDs into short-lasting (5 minutes or less) and long-lasting forms (more than 5 minutes), and further distinguishes each patient as either idiopathic or secondary depending on etiology.

Although most PxDs are primary (idiopathic or genetic), one-fifth of the patients have an identifiable etiology such as cerebrovascular disease, trauma, multiple sclerosis, infections (HIV, cytomegalovirus, syphilis, etc.), kernicterus, Fahr disease, and metabolic disorders.[2-8] Thyrotoxicosis is one of the metabolic causes.[6-8] The association between thyrotoxicosis and choreoathetosis or dystonic posturing was first noted by Gowers in 1893 and usually occurs in young women (14 to 23 years), although middle-aged persons of either sex are sometimes affected.[6-8] The movement disorder usually presents and remits in conjunction with signs of hyperthyroidism. Choreoathetoid movements most commonly affect the distal parts of the limbs more than the proximal parts. The neck and tongue may also be involved. The abnormal movements are usually continuous, but paroxysmal choreoathetosis has also been reported.[9,10] No cerebral lesions have been noted on previous reports on PxD associated with thyrotoxicosis.

The pathophysiology of PxD remains unknown. PKD has been linked to the pericentromeric region of chromosome 16, PNKD is associated with mutations in the myofibrillogenesis regulator 1 (MR-1) gene on the long arm of chromosome 2 (2q32-36 locus), and PED is associated with mutations in the glucose transporter gene, GLUT1, responsible for transport of glucose across the blood-brain barrier.[11,12] Anticonvulsants have been found to be extremely effective in treating PKD and are sometimes useful in other types, suggesting that these disorders may indeed represent forms of channelopathies. Channelopathies may play a role in idiopathic or familial cases, which explains the association of PKD and childhood convulsions, and response to anticonvulsants in certain PKD kindred.[13,14] Impairment of the indirect pathway of the thalamo-cortico-basal circuit due to these channelopathies and/or the disorders causing basal ganglia dysfunction was proposed as the mechanism of the production of PxDs.[15,16] In general, the production of chorea involves dysfunction of the indirect pathway from the caudate and putamen to the internal globus pallidus, whereas dystonia is generated by dysfunction of the direct pathway.

In cases with PxDs of metabolic causes, hormone-mediated changes in the basal metabolic rate or catecholaminergic tone, as well as significant glucose or electrolyte shifts might be expected to affect those cerebral regions with high metabolic rates, such as the basal ganglia. Endocrine and electrolyte abnormalities influence neurotransmitter balance or affect ion channel function and signaling in the basal ganglia.[17] In the absence of structural injury, the changes are usually reversible. Adrenergic blockade with propranolol can also provide symptomatic relief until the hyperthyroidism is definitively treated. Besides, the good response of the PxD to dopamine receptor blockers before the resolution of hyperthyroidism and the presence of decreased concentrations of the dopamine metabolite, homovanillic acid, in the cerebrospinal fluid (CSF) of hyperthyroid patients, suggest that altered dopamine turnover or increased dopamine receptor sensitivity maybe responsible for the attacks.[18]

Familial PNKD is mostly inherited as an autosomal dominant trait, whereas incomplete penetrance has also been reported.[19] It occurs more often in males (male/female ratio: 2/1). The age of onset is usually in the first two decades of life. The frequency of attack varies from three per day to two per year. Precipitating factors are fatigue, alcohol, caffeine, and emotional excitement. The attack usually begins with involuntary movements of an extremity and then it may spread to all extremities and the face. The duration can vary from a few minutes to a few hours. The patient remains conscious and continues to breathe normally during the attack. The attacks are relieved by sleep and respond well to pharmacologic intervention in only a few cases. Clonazepam, diazepam, gabapentin, and levetiracetam can be effective.[4,5,20,21]

Rana *et al*.[22] reported a case of PNKD with a late age of onset and a remote history of Graves' disease requiring total thyroidectomy. Although chronological association is not present between the start of PNKD attacks and the thyrotoxic phase of Grave's disease, autoimmune factors mediating the existence of Grave's disease could be speculated to play a role also in the pathophysiology of PNKD for this case. Atypically, the attacks were reported to occur when the patient was 59 years old, the frequency of attacks ranged from twice per week to five to six times a day, and the duration of attack was shorter than two minutes. In general, PNKDs usually occur at a much younger age and have longer durations of attack with low frequency. Besides, majority of PNKD cases are revealed to be more resistant to pharmacotherapy. Fortunately, administering clonazepam was noted to reduce the symptoms in this case.

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