Diagnosis and treatment of paroxysmal dyskinesias revisited

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***Abstract*:** Paroxysmal dyskinesias (PDs) are a rare group of hyperkinetic movement disorders mainly characterized by their episodic nature. Neurological examination may be entirely normal between the attacks. Three main types of PDs can be distinguished based on their precipitating events - (i) paroxysmal kinesigenic dyskinesias (PKD), (ii) paroxysmal non-kinesigenic dyskinesias (PNKD) and (iii) paroxysmal exercise-induced (exertion-induced) dyskinesias (PED). The diagnosis of PDs is based on their clinical presentation and precipitating events. Substantial progress has been made in the field of genetics and PDs. Treatment options mainly include anticonvulsants and benefit of treatment is depending on the type of PD. Most important differential diagnosis are non-epileptic psychogenic, non-epileptic organic and epileptic attack disorders, especially nocturnal frontal lobe epilepsy.

***Keywords*:** paroxysmal dyskinesia, paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic dyskinesia, paroxysmal exercise-induced (exertion-induced) dyskinesia, epilepsy

Case vignette

A 23-year-old female patient was admitted with brief attacks of motor dysfunction in her lower limbs, which started at age of 10 years. Her attacks were characterized as sudden unilateral stiffness of upper and lower limbs followed by an involuntary extrarotation of the arm and leg. Usually, the right hemibody was involved, but bilateral or alternate manifestation was also perceived. Distinctive attacks were characterized by bizarre, extended, and tossed movements. Consciousness was never impaired. The attacks lasted up to 30 s, the frequency up to 10 times per day.

Sudden movements or emotional stress, sometimes also physical exercise were able to precipitate the attacks. Treatment efforts with clonazepam (1 mg/day) and carbamazepine (250 mg/day) prior to admission led to a significant reduction of frequency (less than 1 attack per day), but sedation and cognitive side effects limited further intake of the medication.

During the grand rounds on the ward one distinct attack could be observed. The patient was emotionally affected because of the planned discharge from our unit. As she stood up from the supine position in her bed, she suddenly developed left-sided hemidystonic and hemichoreatic hyperkinesia with consecutive rotation around the longitudinal body axis with a duration of about 10 s. Consciousness was preserved and she reacted adequately during the attack. The EEG immediately after the attack was normal. In between attacks, we performed neurological and psychic exam as well as other tests including prolonged video-EEG monitoring, cerebral magnetic resonance imaging (cMRI), somatosensory and motor evoked potentials (EPs), and a complete laboratory work up.

The patient's history and the clinical signs during the attack, along with the characteristic precipitating events (sudden movement and emotional stress during the grand rounds) is characteristic for an 'idiopathic paroxysmal kinesigenic dyskinesia.' We started treatment with carbamazepine again, but titration very slowly up to 450 mg/day, which was tolerated well by the patient. The patient has been now free of attacks for a follow-up period of more than 2 years with carbamazepine.

Introduction

Paroxysmal dyskinesias (PDs) are a rare group of movement disorders with typical childhood onset. They are characterized by their episodic nature,

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usually arising out of a background of normal motor activity and behavior. Characteristic clinical features are sudden involuntary abnormal movements, comprising dystonia, chorea, athetosis, and ballism or a combination of these. PD can occur spontaneously or may be precipitated by sudden movements, prolonged exercise, caffeine and alcohol consumption, emotional stress, or fatigue. The duration of attacks can vary and may last from seconds to several hours. Idiopathic (familial and sporadic) forms have to be differentiated from symptomatic ones.

Mount and Reback [1940] coined the term 'familial paroxysmal choreoathetosis' in a seminal description of a family in which a young male had infantile onset of periodic dystonic and choreoathetotic movements, precipitated by alcohol and coffee. Later, Kertesz [1967] reported a group of patients with paroxysmal brief choreoathetosis precipitated by sudden movements and named the condition 'paroxysmal kinesigenic choreoathetosis.' A third form of PD was described by Lance [1977] in a family with attacks precipitated by prolonged exercise, which was further classified as 'paroxysmal exercise-induced dystonia' (PED).

Several classification schemes [Fahn, 1994; Goodenough *et al*. 1978; Lance, 1977] of PD mainly based on duration and etiology have been proposed since the first description by Mount and Reback [1940]. In 1995, Demirkiran and Jankovic proposed a descriptive classification of PD based on precipitating events and differentiated four types: (1) paroxysmal kinesigenic dyskinesias (PKD), (2) paroxysmal non-kinesigenic dyskinesias (PNKD), (3) paroxysmal exercise-induced (exertion-induced) dyskinesias (PED) and (4) paroxysmal hypnogenic dyskinesias (PHD). Further categorization was based on duration of the attacks ($<$ or $>$ 5 min) and presumed etiology, i.e., primary (familial or sporadic) or secondary.

In recent years, considerable progress has been made in the field of genetics in PD. Different genes have been identified for certain forms of PD and, furthermore, clear genotype-phenotype correlations have been reported [Bruno *et al*. 2007].

Hypnogenic paroxysmal dyskinesia has been shown to be a form of frontal lobe epilepsy with excellent response to antiepileptic drug treatment and will not be considered further as a paroxysmal dyskinesia [Meierkord *et al*. 1992; Tinuper *et al*. 1990; Lugaresi and Cirignotti, 1981]. The term 'autosomal dominant nocturnal epilepsy' (ADNFLE) was introduced by Scheffer and coworkers [1994, 1995]. A 'single gene' trait was identified with linkage to chromosome 20q [Phillips *et al*. 1995]. Further gene loci have been linked to chromosomes 15q24 [Phillips *et al*. 1998] and 1q21 [Gambardella *et al*. 2000]. Mutations in two genes encoding different subunits of the neuronal nicotinic acetylcholine receptors (nAChRs) have been replicated [α-subunit (CHRNA4), β-subunit (CHRNB2)]. However, most families do not show any known mutations, giving evidence for at least a fourth locus, which may or may not be related to nAChR [Andermann *et al*. 2005].

Table 1. Distinct features of PKD, PNKD, PED.

	PKD	PNKD	PED
Precipitation	+++	+	+++
Frequency	+++	++	+
Treatment response	+++	++	+
Etiology			
Idiopathic (AD, sporadic)	+++	+++	++
Symptomatic	+	+	(+)

Abbreviations: AD, autosomal dominant; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia; PED, paroxysmal exercise-induced (exertion-induced) dyskinesia; +++ frequent, ++ moderate, + rare, (+) very rare.

Clinical and genetic features of the three main types of PD (PKD, PNKD, PED) will be further discussed in detail [Guerrini *et al*. 2002; Jankovic and Demirkiran, 2002; Nardocci *et al*. 2002; Bhatia, 1999, 2001] (Table 1).

Paroxysmal kinesigenic dyskinesia

PKD comprises sudden attacks of involuntary movements, including dystonia, chorea, athetosis, or ballism precipitated by sudden movement [Kertesz, 1967]. Characteristically, symptoms most commonly occur when a patient stands up quickly or is startled (e.g., 'ringing bell'). Hyperventilation or prolonged physical exercise may also trigger the attacks. Many patients experience an 'aura'-like sensation. Symptoms usually manifest unilaterally, but may alternate or even be bilateral. Limbs are more commonly involved, but neck, face, and trunk may also be affected. Dystonic spasms of the jaw or face may lead to dysarthria. There is a refractory period

after an attack during which sudden movement may not provoke an attack. Consciousness is always preserved. Usually, the attacks last less than 1 min [Bruno *et al.* 2004], although longer durations are also reported [Demirikiran and Jankovic, 1995]. The frequency of attacks is highly variable and can range from 100 per day to less than 1 per month [Bruno *et al.* 2004]. Age of onset is usually in the first or second decade of life, but manifestation in early childhood or late adulthood has been reported [Demirikiran and Jankovic, 1995; Fahn, 1994]. Males are more commonly affected than females with a ratio of 3.75 : 1 [Fahn, 1994]. Mostly, PKDs are idiopathic, and in the majority, there is a family history of autosomal dominant inheritance with penetrance >70%. Sporadic cases are reported frequently [Jankovic and Demirkiran, 2002]. Neurological examination, EEG, and brain imaging between attacks are normal in idiopathic cases.

Some cases of PKD may be symptomatic secondary to multiple sclerosis (MS), brain trauma or endocrine dysfunction [Bhatia, 1999].

Genetics

Although substantial progress has been made with linkage studies to PKD, no causal gene has been identified yet. Linkage to chromosome 16q11.2-q22.1 could be demonstrated in eight Japanese kindreds, one Afro-Caribbean, and one Indian family [Swoboda *et al.* 2000; Valente *et al.* 2000; Tomita *et al.* 1999]. A further locus for PKD has been identified on locus 16p11.2-q11.2 [Bennett *et al.* 2000]. Linkage to both loci could be excluded for an additional family, suggesting the possibility of a third gene for PKD [Spacey *et al.* 2002]. Interestingly, the syndrome of infantile convulsions with paroxysmal choreoathethosis (ICCA) has also been mapped to the region of chromosome 16p [Lee *et al.* 1998; Szepetowski *et al.* 1997]. ICCA is characterized by the occurrence of afebrile convulsions at the age of 3–12 months and variable paroxysmal choreoathetosis. Familial cases are inherited in an autosomal dominant trait with high penetrance. Based on these clinical and linkage findings, ICCA and PKD are regarded as variable clinical expressions of a single genetic disorder [Bennett *et al.* 2000].

Treatment

In contrast to PKND, PKD respond excellent to anticonvulsant treatment [Mink, 2007; Jankovic and Demirkiran, 2002; Bhatia, 1999]. Carbamazepine is reported to be effective in the majority of patients [Demirkiran and Jankovic, 1995]. Bhatia [1999] reported 27 patients with PKD, where 14 patients were treated with carbamazepine, with a significant decrease or disappearance of attacks in 78%. Phenytoin was given in six patients with a good response in three (50%). Clonazepam, sodium valproate, clobazam, diazepam, and benzhexol were tried in one patient each without effect. The effectiveness of carbamazepine and phenytoin was also reported in the largest series of patients with PKD described so far (95 patients) by Bruno *et al.* [2004]. In a Taiwanese study, the benefit of carbamazepine in PKD was also reported, where four of seven patients were prescribed low dose of carbamazepine (1.5–2.0 mg/kg/day) and became free of attacks over a follow-up period of 14–30 months [Tsai *et al.* 2005]. Oxcarbazepine and lamotrigine were also effective in small samples of PKD patients [Tsao, 2004; Uberall and Wenzel, 2000]. The efficacy of topiramate was assessed in eight patients with PKD with a target daily dose of 100–200 mg. Mild side effects were observed and the attacks were optimally controlled in a follow-up period ranging from eight months to two years [Huang *et al.* 2005]. Other drugs used as an alternative treatment for PKD are risperidone [Karakurum *et al.* 2003], acetazolamide, levodopa, flunarizine, and tetrabenazine [Jankovic and Demirkiran, 2002].

In sum, evidence of treatment of PKDs is scarce and mainly coming from single case reports or small open series.

Paroxysmal non-kinesigenic dyskinesia

PNKDs usually occur spontaneously and are not precipitated by sudden movements or physical exertion. Attacks may be triggered by emotional stress, fatigue or consumption of alcohol or caffeine [Mount and Reback, 1940]. Patients often have a combination of involuntary dystonic, choreatic, athetotic, and ballistic movements, mainly affecting the limbs, often unilateral or asymmetric. Like in PKD many patients report an ‘aura’-like sensation (paresthesia, tension in the limbs or dizziness) prior to the onset of the motor manifestation. The attacks usually last between minutes up to 4 h, but both, shorter and longer duration up to days has been reported [Demirkiran and Jankovic, 1995]. The frequency

varies from one to three per day to months of attack-free intervals. The age of manifestation can be in childhood or early teens, and the attacks tend to diminish with age. A male preponderance (1.4 : 1) is described [Fahn, 1994]. Although sporadic cases are reported, PNKD is usually inherited as an autosomal dominant trait with high penetrance (>90%) [Jankovic and Demirkiran, 2002]. Neurological findings, EEG and brain imaging are normal in the idiopathic cases.

Symptomatic PNKD are rare and are most commonly reported in association with MS or vascular thalamic lesions [Berger *et al.* 1984; Lee and Marsden, 1994]. Whether tonic spasms of MS, which are often painful, brief, frequent and stereotyped, represent PNKD or not is discussed controversially [Bhatia, 1999; Berger *et al.* 1984]. Numerous cases with other symptomatic causes are reported (encephalitis, brain trauma, immune-deficiency syndrome, endocrine dysfunction) [Jankovic and Demirkiran, 2002].

Genetics

Linkage to chromosome 2q has been demonstrated for familial PNKD [Fink *et al.* 1996]. Several, but not all studies confirmed these results, raising evidence for genetic heterogeneity of this syndrome [Spacey *et al.* 2006; Matsuo *et al.* 1999; Raskind *et al.* 1998; Fouad *et al.* 1996; Hoefele *et al.* 1997]. Further molecular studies have shown 'missense' mutations in the myofibrillogenesis regulator 1 (MR-1) gene on chromosome 2 (2q32-36 locus) in families with PNKD [Chen *et al.* 2005; Lee *et al.* 2004; Rainier *et al.* 2004]. The function of MR-1 is not fully understood. It is homologous to the hydroxyacetylglutathione hydrolase (HAGH), which catalyses the detoxification of methylglyoxal to lactic acid and reduced gluthatione. Interestingly, methyolglyoxal is reported to be neurotoxic and is found in coffee and alcoholic beverages, which might explain their precipitating effect of attacks in PNKD [Kikuchi *et al.* 1999; Nagao *et al.* 1986]. Recently, Bruno and coworkers [2007] concluded, that PNKD should strictly be defined based on age at onset and ability to precipitate attacks by caffeine and alcohol. Patients with this 'classic' phenotype are likely to harbor MR-1 mutations. Other families with 'atypical' symptoms exist, but are clinically distinct from PNKD and do not have MR-1 mutations. Some of them may represent PED.

An autosomal dominant syndrome of generalized epilepsy and PNKD has been described in one single large European kindred linked to chromonsom 10q22. Sixteen affected individuals over four generations suffering from seizures (absences, rare generalized tonic clonic seizures, or both, $n = 4$), PKND ($n = 7$) or both ($n = 5$) have been described in detail. A mutation in the α-subunit of the large conductance calcium-sensitive potassium (BK) channel was found in this family [Du *et al.* 2005]. The authors suggested that this BK mutation is associated with increased excitability by inducing rapid repolarization of action potentials. This channelopathy links human epilepsy and paroxysmal movement disorders and may give further insight into their pathophysiology.

Treatment

Although PNKD is much more difficult to treat than PKD, anticonvulsants should be tried in every patient [Bhatia, 1999]. Clonazepam may be effective in up to 30% of patients and other anticonvulsants, like carbamazepine, should be considered as further possible treatment option [Bhatia, 1999]. Because PKND may be triggered by emotional stress, fatigue, alcohol or caffeine, the avoidance of these possible precipitating events is recommended [Bhatia, 1999, 2001]. Two case reports have revealed deep brain stimulation as a potential therapeutic option in medically refractory PKND [Yamada *et al.* 2006; Loher *et al.* 2001].

Symptomatic cases may also benefit from benzodiazepines, as described by Mirsattari and coworkers [1999], who reported effectiveness in three of four patients with PKND symptomatic to HIV infection. Levetiracetam was effective in sympomatic PKND secondarily to hypoparathyroidism, where initial treatment with valproic acid failed [Alemdar *et al.* 2007].

Paroxysmal exercise-induced (exertion-induced) dyskinesia

In 1977, Lance described this form of PD in family members, who exhibited longer lasting dystonic attacks, which were precipitated by prolonged physical exercise. PED is less common than PNKD and PKD. Attacks are commonly precipitated by walking or running (lasting >5–20 min), in some cases triggered by exposure to cold [Demirkiran and Jankovic, 1995]. Typically, dystonic movement affecting lower limbs, often bilaterally, is the most common

feature [Bhatia, 1999]. In contrast to PKD and PNKD, 'aura'-like sensations are not reported. The frequency of attacks varies between one per day to one per month. The attacks may last from 5 to 30 min. Age of onset is usually in childhood, but may range from 1 to 30 years. Familial cases of PED have female preponderance [Jankovic and Demirkiran, 2002]. Both, sporadic and familial cases with autosomal dominant mode of inheritance are reported. Neurological examination, EEG, and brain imaging are normal.

Interestingly, PED may be a presenting feature of young-onset idiopathic Parkinson's disease (PD) [Bozi and Bhatia, 2003]. Secondary PED is a rarity and in those cases reported, brain trauma was the underlying etiology [Lim and Wong, 2003; Demirkiran and Jankovic, 1995].

Genetics

Until now, linkage studies of pure PED have been uneventful. Autosomal dominant paroxysmal choreoathetosis/spasticity (CSE), which is characterized by sudden exercise-induced dyskinesia and spastic paraplegia has been mapped to chromosome 1p. A potassium channel gene cluster is known in the vicinity of this gene locus [Auburger *et al*. 1996]. Epilepsy and PD have been reported to co-occur in various forms. Characteristically, epilepsy manifests as idiopathic syndrome, making a genetic cause plausible [Guerrini *et al*. 2000]. A family with Rolando epilepsy with PED and writer's cramp with autosomal recessive inheritance was described by Guerrini and colleagues [1999] and has been linked to chromosome 16p, which is within the ICCA region. A clinical syndrome associating absences and PED was reported by Guerrini and colleagues [2000]. Six sporadic patients with pyknoleptic absences developed PD, with PED in 50% of patients. Both, epileptic seizures and PED had good prognosis. Recently, Kamm and coworkers [2007] described a family with four affected members over three generations and probable autosomal dominant inheritance with PED, generalized epilepsy, developmental delay and migraine in variable combinations. Linkage to chromosomes 2 and 16 was excluded, suggesting a further yet unknown underlying genetic basis.

Treatment

Avoiding precipitating events, like prolonged physical exercise, may prevent attacks. Anticonvulsants were not overall useful, although clonazepam and carbamazepine were found to be of limited benefit [Bhatia, 1997; Demirkiran and Jankovic, 1995]. Levodopa, acetazolamide, and trihexiphenidyl were not usually successful, except in isolated cases [Bhatia, 1997].

Conclusion

PDs are rare neurological disorders, characterized by a sudden onset of dystonic, choreatic, athetotic, and ballistic movements with variable underlying mechanisms. Three main groups of PD can be distinguished mainly based on the precipitating events. Most PDs have an idiopathic (familial and sporadic) etiology, although rare symptomatic forms are reported. Treatment success depends on the type of PD, where patients with PKD have the best chance to benefit with anticonvulsant treatment.

Substantial progress has been made in the field of genetics and PDs. Linkage studies could disclose gene loci on chromosome 16 in PKD, but, until now, no specific gene has been identified. In PKND, genotype predicts phenotype and in most cases of PKND an ion-channel dysfunction is not evident.

Conflict of interest statement

None declared.

References

Alemdar, M., Iseri, P., Selekler, M. and Komsuoglu, S.S. (2007) Levetiractam responding paroxysmal nonkinesigenic dyskinesia. *Clin Neuropharmacol* 30(4): 241–244.

Andermann, F., Kobayashi, E. and Andermann, E. (2005) Genetic focal epilepsies: state of the art and paths to the future. *Epilepsia* 46(Suppl 10): 61–67.

Auburger, G., Ratzlaff, T., Lunkes, A., Nelles, H.W., Leube, B., Binkofski, F. *et al*. (1996) A gene for autosomal dominant paroxysmal choreoathetosis/spasticity (CSE) maps to the vicinity of a potassium channel gene cluster on chromosome 1p, probably within 2 cM between D1S443 and D1S197. *Genomics* 31: 90–94.

Bennett, L.B., Roach, E.S. and Bowcock, A.M. (2000) A locus for paroxysmal kinesigenic dyskinesia maps to human chromosome 16. *Neurology* 54: 125–130.

Berger, J.R., Sheremata, W.A. and Melamed, E. (1984) Paroxysmal dystonia as the initial manifestation of multiple sclerosis. *Arch Neurol* 41: 747–750.

Bhatia, K.P., Soland, V.L., Bhatt, M.H., Quinn, N.P. and Marsden, C.D. (1997) Paroxysmal exercise-induced dystonia: eight new sporadic cases and a review of the literature. *Mov Disord* 12(6): 1007–1012.

Bhatia, K.P. (1999) The paroxysmal dyskinesias. *J Neurol* 246: 149–155.

Bhatia, K.P. (2001) Familial (idiopathic) paroxysmal dyskinesias: an update. *Semin Neurol* 21: 69–74.

Bozi, M. and Bhatia, K.P. (2003) Paroxysmal exercise induced dystonia as a presenting symptom of young onset Parkinsonsás disease. *Mov Disord* 18(12): 1545–1547.

Bruno, M.K., Hallett, M., Gwinn-Hardy, K., Sorensen, B., Considine, E., Tucker, S. *et al.* (2004) Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. *Neurology* 63: 2280–2287.

Bruno, M.K., Lee, H.Y., Auburger, G.W., Friedman, A., Nielsen, J.E., Lang, A.E. *et al.* (2007) Genotype-phenotype correlation of paroxysmal nonkinesigenic dyskinesia. *Neurology* 68(21): 1782–1789.

Chen, D.H., Matsushita, M., Rainier, S., Meaney, B., Tisch, L., Feleke, A. *et al.* (2005) Presence of alanine-to-valine substitutions in myofibrillogenesis regulator 1 in paroxysmal nonkinesigenic dyskinesia: confirmation in 2 kindreds. *Arch Neurol* 62: 597–600.

Demirkiran, M. and Jankovic, J. (1995) Paroxysmal dyskinesias: clinical features and classification. *Ann Neurol* 38: 571–579.

Du, W., Bautista, J.F., Yang, H., Diez-Sampedro, A., You, S.A., Wang, L. *et al.* (2005) Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. *Nature Genetics* 37: 733–738.

Fahn, S. (1994) The paroxysmal dyskinesias. In: Marsden, C.D. and Fahn, S. (eds) Movement disorders 3. Butterworth-Heinemann, Oxford, pp. 310–345.

Fink, J.W., Rainer, S., Wilkowski, J., Jones, S.M., Kume, A., Hedera, P. *et al.* (1996) Paroxysmal dystonic choreoathetosis: tight linkage to chromosome 2q. *Am J Hum Genet* 59: 140–145.

Fouad, G.T., Servidei, S., Durcan, S., Bertini, E. and Ptacek, L.J. (1996) A gene for familial paroxysmal dyskinesia (FPD1) maps to chromosome 2q. *Am J Hum Genet* 59: 135–139.

Gambardella, A., Annesi, G., De Fusco, M., Patrignani, A., Aguglia, U., Annesi, F. *et al.* (2000) A new locus for autosomal dominant nocturnal frontal lobe epilepsy maps to chromosome 1. *Neurology* 55: 1467–1471.

Goodenough, D.J., Fariello, R.G., Annis, B.L. and Chun, R.W. (1978) Familial and aquired paroxysmal dyskinesias. A proposed classification with delineation of clinical features. *Arch Neurol* 35: 827–831.

Guerrini, R., Sanchez-Carpintero, R., Deonna, T., Santucci, M., Bhatia, K.P., Moreno, T. *et al.* (2000) Early-onset absence epilepsy and paroxysmal dyskinesia. *Epilepsia* 43(10): 1224–1229.

Guerrini, R., Bonanni, P., Nardocci, N., Parmeggiani, M., Piccirilli, M., De Fusco, P. *et al.* (1999) Autosomal recessive rolandic epilepsy with paroxysmal exercise induced dystonia and writer's cramp: deliniation of the syndrome and gene mapping to chromosome 16p12-11.2. *Ann Neurol* 45: 344–352.

Guerrini, R., Parmeggiani, L. and Casari, G. (2002) Epilepsy and paroxysmal dyskinesia: co-occurrence and differential diagnosis. In: Fahn, S. (ed.) *Myoclonus and paroxysmal dyskinesias, advances in neurology.* Vol 89. Lippincott Williams & Wilkins, Philadelphia, pp. 433–443.

Hoefele, K., Benecke, R. and Auburger, G. (1997) Gene locus FPD1 of the dystonic Mount-Reback type of autosomal dominant paroxysmal choreoathetosis. *Neurology* 49: 1252–1256.

Huang, Y.G., Chen, Y.C., Du, F., Li, R., Xu, G.L., Jiang, W. *et al.* (2005) Topiramate therapy for paroxysmal kinesigenic choreoathetosis. *Mov Disord* 20(1): 75–77.

Jankovic, J. and Demirkiran, M. (2002) Classification of paroxysmal dyskinesias and ataxias. In: Fahn, S. (ed.) *Myoclonus and Paroxysmal Dyskinesias, Advances in Neurology.* Vol 89. Lippincott Williams & Wilkins, Philadelphia, pp. 387–400.

Kamm, C., Mayer, P., Sharma, M., Niemann, G. and Gasser, T. (2007) New family with paroxysmal exercise induced dystonia and epilepsy. *Mov Disord* 22(6): 873–877.

Karakurum, B., Karatas, M. and Yildirim, T. (2003) Risperidone as an alternative treatment for paroxysmal kinesigenic dyskinesia. *Neurol Sci* 24(2): 92–93.

Kertesz, A. (1967) Paroxysmal kinesiogenic choreoathetosis. An entity within the paroxysmal choreoathetosis syndromes. Description of 10 cases, included 1 autopsied. *Neurology* 17: 680–690.

Kikuchi, S., Shinpo, K., Moriwaka, F., Makita, Z., Miyata, T. and Tashiro, L. (1999) Neurotoxicity of methylglyoxal and 3-deoxyglucosone on cultured cortical neurons: synergism between glycation and oxidative stress, possibly involved in neurodegenerative diseases. *J Neurosci Res* 57: 280–289.

Lance, J.W. (1977) Familial paroxysmal dystonic choreoathetosis and its differentiation from related syndromes. *Ann Neurol* 2: 285–293.

Lee, M.S. and Marsden, C.D. (1994) Movement disorders following lesions of the thalamus or subthalamic region. *Mov Disor* 9: 493–507.

Lee, W.L., Tay, A., Ong, H.T., Goh, L.M., Monaco, A.P. and Szepetowski, P. (1998) Association of infantile convulsions with paroxysmal dyskinesias (ICCA syndrome): confirmation of linkage

to human chromosome 16p12-q12 in a Chinese family. *Hum Genet* 103: 608–612.

Lee, H.Y., Xu, Y., Huang, Y., Ahn, A.H., Auburger, G.W., Pandolfo, M. *et al*. (2004) The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway. *Hum Mol Genet* 13: 3161–3170.

Lim, E.C. and Wong, S. (2003) Posttraumatic paroxysmal exercise-induced dystonia: case report and review of the literature. *Parkinsonism Related Disord* 9: 371–373.

Loher, T.J., Krauss, J.K., Burgunder, J.M., Taub, E. and Siegfried, J. (2001) Chronic thalamic stimulation for treatment of dystonic paroxysmal nonkinesigenic dyskinesia. *Neurology* 56(2): 268–270.

Lugaresi, E. and Cirignotti, F. (1981) Hypnogenic paroxysmal dystonia: epileptic seizure or a new syndrome. *Sleep* 4: 129–138.

Matsuo, H., Kamakuro, K., Saito, M., Okano, M., Nagase, T., Tadano, Y. *et al*. (1999) Familial paroxysmal dystonic choreoathetosis: clinical findings in a large Japanese family and genetic linkage to 2q. *Arch Neurol* 56: 721–726.

Meierkord, H., Fish, D.R., Smith, S.J.M., Scott, C.A., Shorvon, S.D. and Marsden, C.D. (1992) Is nocturnal dystonia a form of frontal lobe epilepsy? *Mov Disord* 7: 38–42.

Mink, J.W. (2007) The paroxysmal dyskinesias. *Current Opin Pediatr* 19: 652–656.

Mirsattari, S.M., Berry, M.E., Holden, J.K., Ni, W., Nath, A. and Power, C. (1999) Paroxysmal dyskinesias in patients with HIV infection. *Neurology* 52(1): 109–114.

Mount, L.A. and Reback, S. (1940) Familial paroxysmal choreoathetosis. *Arch Neurology Psychiatry* 44: 841–847.

Nagao, M., Fujita, Y., Wakagayadhi, K., Nukaya, H., Kosuge, T. and Sugimura, T. (1986) Mutagens in coffee and other beverages. *Environ Health Perspect* 67: 89–91.

Nardocci, N., Fernandez-Alvarez, E., Wood, N.W., Spacey, S.D. and Richter, A. (2002) The paroxysmal dyskinesias. In: Guerrini, R., Aicardi, J., Andermann, F. and Hallett, M. (eds) *Epilepsy and Movement Disorders*. Cambridge University Press, Cambridge, pp. 125–139.

Phillips, H.A., Scheffer, I.E., Berkovic, S.F., Holloway, G.E., Sutherland, G.R. and Mulley, J.C. (1995) Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q 13.2. *Nat Gen* 10: 117–118.

Phillips, H.A., Scheffer, I.E., Crossland, K.M., Bhatia, K.P., Fish, D.R., Marsden, C.D. *et al*. (1998) Autosomal dominant nocturnal frontal lobe epilepsy: genetic heterogeneity and evidence for a second locus at 15q24. *Am J Hum Genet* 63: 1108–1116.

Rainier, S., Thomas, D., Tokarz, D., Ming, L., Bui, M., Plein, E. *et al*. (2004) Myofibrillogenesis regulator 1 gene mutations cause paroxysmal dystonic choreoathetosis. *Arch Neurol* 61: 1025–1029.

Raskind, W.H., Bolin, T., Wolff, J., Fink, J., Matsushita, M., Litt, M. *et al*. (1998) Further localization of a gene for paroxysmal dystonic choreoathetosis to a 5 cM region on chromosome 2q34. *Hum Genet* 102: 93–97.

Scheffer, I.E., Bhatia, K.P. and Lopes-Cendes, I. (1994) Autosomal dominant frontal lobe epilepsy misdiagnosed as a sleep disorder. *Lancet* 343: 515–517.

Scheffer, I.E., Bhatia, K.P. and Lopes-Cendes, I. (1995) Autosomal dominant nocturnal frontal lobe epilepsy. A distince clinical disorder. *Brain* 118: 61–73.

Spacey, S.D., Valente, M., Wali, G.M., Warner, T.T., Jarman, P.R., Schapira, A.H. *et al*. (2002) Genetic and clinical heterogeneity in paroxysmal kinesigenic dyskinesia: evidence for a third EKD gene. *Mov Disord* 17: 717–725.

Spacey, S.D., Adams, P.J., Lam, P.C., Materek, L.A., Stoessl, A.J., Snutch, T.P. *et al*. (2006) Genetic heterogeneity in paroxysmal nonkinesigenic dyskinesia. *Neurology* 66(10): 1588–1590.

Swoboda, K.J., Soong, B., McKenna, C., Brunt, E.R., Litt, M., Bale Jr, J.F. *et al*. (2000) Paroxysmal kinesigenic dyskinesia and infantile convulsions: clinical and linkage studies. *Neurology* 55: 224–230.

Szepetowski, P., Rochette, J., Berquin, P., Piussan, C., Lathrop, G.M. and Monaco, A.P. (1997) Familial infantile convulsions and paroxysmal choreoathetosis: a new neurological syndrome linked to the pericentromeric region of human chromosome 16. *Am J Hum Genet* 61: 889–898.

Tomita, H., Nagamitsu, S., Wakui, K., Fukushima, Y., Yamada, K., Sadamatsu, M. *et al*. (1999) Paroxysmal kinesigenic choreoathetosis locus maps to chromosome 16p11.2-q12.1. *Am J Hum Genet* 65: 1688–1697.

Tinuper, P., Cerullo, A., Cirignotti, F., Cortelli, P., Lugaresi, E. and Montagna, P. (1990) Nocturnal paroxysmal dystonia with short lasting attacks: three cases with evidence for an epileptic frontal lobe origin of seizures. *Epilepsia* 31: 549–556.

Tsai, J.D., Chou, I.C., Tsai, F.J., Kuo, H.T. and Tsai, C.H. (2005) Clinical manifestation and carbamazepine treatment of patients with paroxysmal kinesigenic choreoathetosis. *Acta Paediatr Taiwan* 46(3): 138–142.

Tsao, C.Y. (2004) Effective treatment with oxcarbazepine in paroxysmal kinesigenic choreoathetosis. *J Child Neurol* 19(4): 300–301.

Uberall, M.A. and Wenzel, D. (2000) Effectiveness of lamotrigine in children with paroxysmal

kinesigenic choreoathetosis. *Dev Med Child Neurol* 42(10): 699–700.

Valente, E.M., Spacey, S.D., Wali, G.M., Bhatia, K.P., Dixon, P.H., Wood, N.W. *et al.* (2000) Second paroxysmal kinesigenic choreoathetosis locus (EKD2) mapping on 16q13-q22.1 indicates a family of genes which give rise to paroxysmal disorders on human chromosome 16. *Brain* 123 (Pt 10): 2040.

Yamada, K., Goto, S., Soyama, N., Shimoda, O., Kudo, M., Kuratsu, J. *et al.* (2006) Complete suppression of paroxysmal nonkinesigenic dyskinesia by globus pallidus internus pallidal stimulation. *Mov Disord* 21(4): 576–579.