17 Paroxysmal Movement Disorders

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Introduction

The paroxysmal dyskinesias are a rare group of conditions manifesting as abnormal involuntary movements that recur episodically and last only a brief duration.[1] The conditions may be inherited or acquired. The abnormal movements may be choreic, dystonic, ballistic or a mixture of these.[1] Between episodes, the patient is generally normal. Misdiagnosis is thus quite common. Recently many advances have taken place regarding the genetics and pathophysiological mechanisms of these conditions.[2]

Historical Aspects and Classification

Mount and Reback first used the term paroxysmal dystonic choreoathetosis (PDC) describing episodes of "choreo-dystonia" in a 23 year old man[3] lasting several hours precipitated by drinking alcohol and coffee.[3,4] Other family members were similarly affected in an autosomal dominant pattern. Subsequently other families were also reported with similar descriptions.[4,5]

Kertesz (1967) described paroxysmal kinesigenic choreoathetosis (PKC)[7] in which attacks were induced by sudden movement. It became clear that this disorder responded well to antiepileptic drugs, particularly carbamazepine.[8] Lance (1977)[9] classified the paroxysmal dyskinesias based primarily on duration of attacks into three types:

- PKC - in which there were brief attacks up to 5 minutes induced by sudden movement
- PDC - in which attacks were not induced by sudden movement and were of long duration up to 4 hours
- PED - a third form in which attacks were induced by prolonged exercise.

Demerkirin and Jankovic[10] more recently suggested replacing the term 'choreoathetosis' with dyskinesias and grouping these conditions into two broad groups namely 'paroxysmal kinesigenic dyskinesia' (PKD) if the disorder was induced by sudden movement and 'paroxysmal non-kinesigenic dyskinesia' (PKND) if it was not. These terms broadly correlate with the PKC and PDC of the Lance classification. Cases could also be described as either idiopathic (sporadic or familial) or secondary or symptomatic due to a variety of aetiologies.

Clinical Features

Paroxysmal Kinesigenic Dyskinesia (PKD or PKC)

In this condition, brief dyskinetic episodes are precipitated by sudden movement.[7] Onset is from early childhood (mean 13 years)[11] with a notable predominance of males. Most cases are idiopathic and apparently sporadic. An autosomal dominant family history is present in about 23% of cases.[11] The attacks usually unilateral, frequently manifest as dystonia and are induced by a sudden change in position, classically from a sitting to standing. However, even startle, continuous exercise or a sudden change in velocity can trigger them and, rarely, they can occur in sleep. A preceding 'aura-like' sensation in the limb which gets involved in an attack has been reported in 63% of cases with PKD.[11] Rarely the episodes can generalize. Speech can be affected but consciousness is not lost. Typically PKD attacks are very brief usually seconds to 1-2 minutes, with many attacks per day. After an attack there is usually a short refractory period. Some patients can abort an attack by stopping moving or warming up slowly.

PKD patients respond dramatically to low doses of antiepileptic drugs with a particular sensitivity to carbamazepine which is the drug of choice.[8,11]

The attack frequency of PKD wanes over time decreasing considerably or abating in adulthood.

An association with epilepsy has been recognized in some familial cases with PKD. Families with an affected with infantile convulsions with later onset of episodes of paroxysmal choreoathetosis (called **i**nfantile **c**onvulsions and **c**horeo**a**thetosis syndrome or **ICCA** syndrome) have been reported linked to the pericentromic region of chromosome 16p12-q12.[12,13] Families with typical PKD with or without epilepsy have now also been linked to the same region of chromosome 16.[14.16]

Paroxysmal Non-Kinesigenic Dyskinesia (PNKD or PDC)

Idiopathic PNKD also has its onset in childhood or adolescence with intermittent episodes of dystonia/chorea lasting many hours[17] and frequently precipitated by stress, fatigue, alcohol or coffee.[3] Unlike PKD the episodes are infrequent with long attack-free intervals. As with PKD more males than females are affected (1.4:1) and attacks wane with age.[17]

An autosomal dominant pattern of inheritance has been noted in all reported families with typical PNKD.[4,18-21] A family with PDC with interictal myokymia[22] and another with spasticity referred to as **CSE** (choreoathetosis/spasticity, episodic movement disorder) have been reported.[23]

Patients usually do not benefit from antiepileptic drugs like carbamazepine, although some patients may respond to levodopa.[24]

Two groups separately linked families with autosomal dominant PNKD to chromosome 2q and all families with typical autosomal dominant PNKD from around the world were linked to the same locus.[19,20] Recently the gene for this disorder has been identified and is called the **myofibrillogenesis regulator 1 gene** (see genetic section). Not surprisingly, the family with the CSE syndrome has been linked to different locus on chromosome 1p but the gene is yet unknown.[23]

Paroxysmal Exercise-induced Dyskinesia (PED)

PED is distinct from the kinesigenic form in that the attacks come on after 10-15 minutes of continuous exercise rather than at the initiation of movement.[25] The attacks are usually dystonic and appear in the body part involved in the exercise, most commonly the legs, but focal jaw dystonia after chewing gum has been reported.[26] It can also be triggered by cold,[27] passive movements and vibration,[28] and TMS.[29]

Linkage to the PNKD locus on chromosome 2q has been excluded in a PED family.[26] However, a recessive family with rolandic epilepsy, episodic exercise-induced dystonia and writers cramp (**RE-PED-WC** syndrome) has been linked to chromosome 16p 12-11.2[31] in the same region of as the families with the ICCA syndrome[12,13] and PKD suggesting an overlap between these disorders.

Anticonvulsants are only occasionally useful in PED.[25] Levodopa is sometimes beneficial as is acetazolamide and trihexiphenidyl.[25]

Paroxysmal Hypnogenic Dyskinesia (PHD*)*

In this condition episodes of paroxysmal dyskinesia occur in sleep, hence the term ‘hypnogenic’. Lugaresi and Cirignotta (1981) described five patients who had attacks almost every night.[32] Typically, the patient awakes and has involuntary dystonic and ballistic thrashing movements of the limbs lasting up to 45 seconds, usually with no detectable concurrent EEG abnormalities. Several attacks can occur each night. Sporadic and familial cases have been described.[33-36] This disorder was initially misdiagnosed as a type of sleep disorder.[36] It is now clear that most of these cases are due to mesial frontal lobe seizures.[34,35] ADNFLE (**a**utosomal **d**ominant **n**octurnal **f**rontal **l**obe **e**pilepsy) was the eponym given to describe this condition in six families in whom affected members had typical PHD attacks.[35] The gene responsible for ADNFLE has been discovered in a few families (see genetics section). Antiepileptic drugs, particularly carbamazepine, are very effective in most cases.[35]

Pathophysiology

The paroxysmal dyskinesias have many similarities to other episodic disorders of the nervous system such as **episodic ataxias** and **periodic paralyses**, suggesting a common pathophysiological

mechanism.[2] More and more paroxysmal neurological disorders are being discovered to be due to genetic mutations regulating ion channels called **channelopathies**.[45-50] The periodic paralyses were found to be caused by mutations in voltage-gated sodium[47] and calcium[48] channels. Subsequently, the two forms of episodic ataxia (EA1 and EA2) were shown to be due to mutations of voltage-gated potassium[45] and calcium channels.[50] There are similarities between PKD and episodic ataxia type 1 (EA1).[45] EA1 attacks are also frequently provoked by kinesigenic stimuli, similar to PKD, and episodes are also brief and frequent.[51] Both conditions have an early age of onset and both have the tendency to abate in adulthood. Although EA1 typically responds to acetazolamide, like PKD, antiepileptic drugs may reduce EA1 attacks in some patients and also help the interictal myokymia seen in this disorder.[51,52]

Thus, like the periodic paralyses and episodic ataxias, the familial paroxysmal dyskinesias may also be due to defects in genes regulating ion channels.[2]

Genetics (Table 1)

Paroxysmal Non-kinesigenic Dyskinesia (PNKD)

Two separate groups reported linkage to microsatellite markers on distal 2q (2q31-q36).[20,21] This was further confirmed in a British family,[53] a North American family of German descent and a Japanese family, all with typical PNKD with autosmal dominant inhertitance.[53-55] It appears that there is genetic homogeneity for typical familial PNKD/PDC. The gene for this disorder was recently identified and is called the **myofibrillogenesis regulator 1 gene**.[56] Mis-sense mutations were identified in the affected subjects from two unrelated families.[57] Further confirmation was obtained in 50 individuals from eight families.[58] The mutations cause changes (Ala to Val) in the N-terminus of two MR-1 isoforms. The MR-1L isoform is specifically expressed in brain and is localized to the cell membrane while the MR-1S isoform is ubiquitously expressed and shows diffuse cytoplasmic and nuclear localization. Bioinformatic analysis reveals that the MR-1 gene is homologous to the hydroxyacylglutathione hydrolase (HAGH) gene. HAGH functions in a pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a by-product of oxidative stress.[58] These results suggest a mechanism whereby alcohol, coffee and stress may act as precipitants of attacks in PNKD.[58]

PKD/ ICCA syndrome/ Rolandic Epilepsy, Paroxysmal Exercise-induced Dystonia and Writers Cramp (RE-PED-WC syndrome)

All three of these disorders are linked to the same pericentromic region of chromosome 16 and thus are considered together. Szepetowski and colleagues (1998) first linked four French families with what they described as the 'ICCA syndrome' to the pericentromeric region of chromosome 16.[12] Subsequently, linkage to the same locus was further confirmed in a Chinese family said to have a similar disorder.[13] Although the clinical description of the paroxysmal dyskinetic episodes in these reports was rather limited, it seemed similar to PKD. Not surprisingly, a report of eight Japanese families[14] and an African-American kindred,[15] all with typical PKC, were linked to the pericentromeric region of chromosome 16. Furthermore, the autosomal recessive family with rolandic epilepsy, paroxysmal exercise-induced dyskinesia and writers cramp (RE-PED-WC) syndrome has also been linked to chromosome 16 within the ICCA region.[31] An Indian family with PKC has been linked to a second locus on chromosome 16q distinct from the locus of the Japanese families with PKC thus suggesting that there may be a family of genes causing paroxysmal disorders on the pericentromic region of chromosome 16.[16] Different candidate genes including ion channel genes have been excluded[58] but the gene is still to be found. Furthermore, there are families with PKC which do not link to chromosome 16[59] suggesting at least one more locus and confirming that PKD is genetically heterogeneous.

Table 1 Mapped loci/genes for familial paroxysmal dyskinesias

Condition	*Chromosome*	*Gene*	*Gene Mechanism/Channel*
PNKD			
Familial paroxysmal non-kinesigenic dyskinesia (PNKD)	2q33-35	MR 1 gene	Stress response pathway gene
Paroxysmal choreoathetosis/spasticity	1p	Not known	Not known
PKD/ICCA			
Infantile convulsions & paroxysmal choreoathetosis (ICCA)	16p12-q12	Not known	Not known
Familial paroxysmal kinesigenic dyskinesias (PKD)	16p11.2-q12.1	Not known	Not known
PED			
Autosomal recessive RE-WC-PED syndrome	16p12-11.2	Not known	Not known
HPD			
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	20q13	CHRNA4	Ach receptor
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	15q24	?CHRNA3	?Ach receptor

RE-WC-PED = Rolandic epilepsy, writers cramp and paroxysmal exercise-induced dystonia syndrome;
Ach= Nicotinic acetylcholine receptor

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)

In an Australian family, Phillips et al (1995) mapped a ADNFLE locus on chromosome 20q13.2 and the obvious candidate was the alpha 4 subunit of the neuronal acetylcholine receptor (CHRNA4) gene.[60] Two different mutations (a mis-sense mutation and a 3-bp insertion) were then identified in the CHRNA4 gene in the Australian family and in a Norwegian family respectively.[61,62] However, another family with ADNFLE was not linked to CHRNA4 on chromosome 20q but to a novel locus on chromosome 15q24 close to a CHRNA3/CNRNA5/CHRNB4 nicotinic acetylcholine receptor gene cluster.[63] Also, in seven other families with ADNFLE and in seven sporadic cases, linkage to the ADNFLE loci on chromosome 20q13.2 and 15q24 was excluded, suggesting the existence of at least a third ADNFLE locus and supporting the fact that ADNFLE is a genetically heterogeneous disease.[63]

Summary

The paroxysmal dyskinesias are an heterogeneous group of disorders that have the shared feature of an episodic hyperkinetic movement disorder. There are many similarities between the paroxysmal dyskinesias and other intermittent neurological disorders like periodic paralyses, episodic ataxias and migraine suggesting a common pathophysiology. It is likely that the paroxysmal dyskinesias, like these other conditions, are also caused by defective ion channel genes. The list of linked gene loci causing the paroxysmal dyskinesia phenotypes is growing rapidly (Table 1) although the genes for most of these conditions, apart from PNKD and ADNFLE, are still to be identified. Finding the genes will result in better understanding of the pathophysiology, classification and treatment of these curious disorders.

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