PAROXYSMAL DYSKINESIAS

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Paroxysmal movement disorders are conditions characterized by bouts of abnormal involuntary movements with sudden onset and brief but variable duration, and no change in consciousness [1]. The episodic involuntary movements can be dystonic, choreoform or ballistic, or a complex combination of these, hence referred to as *paroxysmal dyskinesias* (PxD). These are relatively rare disorders but exact prevalence remains unclear. The classification of PxDs by Demirkiran and Jankovic is mainly based on the difference of precipitating factors and recognizes 3 subtypes comprising paroxysmal kinesigenic (PKD), non-kinesigenic (PNKD), and exercise-induced (PED) dyskinesia while the time factor is also crucial. Each of the three major types of PxD have been further classified as either idiopathic or symptomatic, depending on the etiology. A list of reported secondary causes of PxD is provided in Table 1 and the differential diagnosis of these forms will be discussed including the psychogenic forms. A number of genes responsible for the “idiopathic” forms of PxD have now been recognized and therefore genotype-phenotype correlations have become clear and will be discussed.

In addition to the classic forms of PxD two other conditions need to be mentioned in the differential as they have paroxysmal involuntary movements. These include alternating hemiplegia of childhood (AHC) and Allan-Herndon-Dudley syndrome (monocarboxylate transporter 8 deficiency), the genetic bases of which have been recently elucidated. The other group of disorders which should be mentioned is the Episodic Ataxias (EA).

PAROXYSMAL KINESIGENIC DYSKINESIA

Kertesz in 1967 described this as a form of *paroxysmal kinesigenic choreo-athetosis*. By definition, PKD episodes are triggered by sudden movements like initiation of standing, walking, or running or even intention to move and acceleration. PKD typically has a male preponderance (3:1) with onset during childhood or early adolescence. As per definition PKD attacks are brought on by a sudden movement but also increase in speed, amplitude, force strength, or sudden addition of new actions. An aura, either paresthesias or sensations of muscular tension may preceding the attack.

PKD attacks often are dystonic but chorea or ballismus may occur. The distribution often is hemibody including face but attacks may be generalized. Speech disturbance can occur. Attacks are usually very brief just seconds in most cases. Attacks are frequent upto 20-30 a day in some cases, however after the mid 20’s the attack frequency can diminish and even full remissions can occur. PKD attacks usually respond dramatically to anticonvulsants, primarily carbamazepine, which is the drug of choice usually in low doses (50-200 mg daily). Oxcarbazepine, phenytoin, hydantoin, and topiramate, as well as barbiturates, have been also reported to be beneficial.

Familial PKD is inherited in an autosomal dominant fashion. An association of familial PKD with benign familial infantile convulsions (BFIS) was recognized leading to identification of a common locus in the pericentric region of chromosome 16 suggested allelism of these two disorders. More recently using whole exome sequencing heterozygous mutations in *PRRT2*, a gene encoding the proline-rich transmembrane protein 2, has been identified as the cause of PKD as well as BFIS.

The majority of the *PRRT2* patients are of far-east ancestry. Caucasian patients represented the second most common ancestry. By far the most common mutation accounting for approximately half of these patients is the c.649dupC mutation, but other truncating mutations have been described and are predicted to result in haploinsufficiency. Phenotypic missense variants (possibly with reduced penetrance) and microdeletions have also been reported. The *PRRT2* gene encodes a protein that is highly expressed throughout the nervous system. To date, the function of *PRRT2* is poorly understood. There is evidence for an interaction with synaptosomal associated protein 25 (SNAP-25), suggesting disrupted neurotransmission from synaptic vesicles at the presynaptic membrane.

The discovery of the gene has led to an expansion of the phenotypic spectrum associated with *PRRT2* gene mutations and migraine, hemiplegic migraine, episodic ataxia, febrile seizures, sporadic infantile convulsions, and paroxysmal torticollis of the infancy - alone or in various combinations have all been reported.

Comparison of patients with and without *PRRT2* mutations shows that *PRRT2* positive cases are younger at symptom onset, have more frequently presence of premonitory sensation and can also have additional features including seizure, and migraine compared with patients without *PRRT2* mutation. Most *PRRT2* mutation carriers respond completely to low-dose carbamazepine while the majority of the negative PRRT2 cases do not have a full response to carbamazepine.

PAROXYSMAL NON-KINESIGENIC DYSKINESIA

Mount and Reback gave the first clear description, which they named *familial paroxysmal choreoathetosis* in a large family with 28 affected members in five generations. Typically, attacks were precipitated by alcohol, coffee, fatigue, emotional stress, and with improvement after rest and sleep and attacks are of long duration of several hours.

Age at onset is in childhood, and only a few patients have onset after 18 years of age. Attacks are typically characterized by a combination of dystonia and chorea and can be unilateral or generalized and speech impairment can occur. A number of patients have an aura as vague weakness, shortness of breath, and migraine. Frequency of attacks is infrequent but variable ranging from several per day to just one over a lifetime. Many are able to control their attacks by avoiding precipitants. Clonazepam or diazepam, taken both as a prophylactic and as an abortive agent, usually produces a reasonable benefit. Like PKD attack frequency decreases with aging and remissions may occur. Two independent studies detected heterozygous mutations in the myofibrillogenesis regulator gene (*MR-1*) in several families with PNKD in 2004. Several subsequent reports have confirmed *MR-1* mutations as the most common cause of PNKD. Genetic heterogeneity has been described and in 2005 a missense mutation of the *KCNMA1* gene was detected in a large family with complicated phenotype with PNKD but also epileptic seizures.

The *MR-1* gene on chromosome 2q35 encodes for a protein with 3 isoforms with different cellular distribution and presumably distinct biological functions However, details of its function are not yet known. *MR-1* is a homologue of the hydroxyacylglutathione hydrolase (*HAGH*) gene, which plays a role in the pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic drinks and produced as a by-product of oxidative stress therefore suggesting a possible mechanism whereby alcohol, coffee, and stress may induce attacks in these patients.

Patients with *MR-1* mutations have three distinguishing features: 1) onset of attacks in infancy or early childhood; 2) precipitation of attacks by caffeine and alcohol; and 3) a favorable response to benzodiazepines and sleep. In contrast, patients with PNKD who did not carry a *MR-1* mutation were more variable in their age of onset, provoking factors, and response to medication.

PAROXYSMAL EXERCISE-INDUCED DYSKINESIA

Lance delineated paroxysmal exercise-induced dyskinesias (PED) as an “intermediate type” of paroxysmal dystonic choreoathetosis distinct from both PKD and PNKD. Attacks were longer in duration compared to PKD but shorter than PNKD and were not precipitated by alcohol, stress, or anxiety, nor induced by sudden movements but triggered by continuous exertion typically walking, running. An autosomal dominant inheritance was noted in the familial cases but sporadic cases are common.

Recently, mutations in the *SLC2A1* gene encoding for glucose transport protein type 1 (GLUT1) were detected in several families and sporadic patients with PED. PED may present the sole clinical feature without any accompanying clinical signs or be part of the complex phenotypic spectrum of GLUT1 deficiency syndrome

Phenotype-genotype correlations exist for *SLC2A1* gene defects, with splice site, nonsense, insertions, deletions (i.e. loss of function mutations) being associated with younger age at onset and a more severe clinical phenotype of GLUT1 deficiency syndrome, including epilepsy, hypotonia, spasticity, ataxia, and developmental delay, compared with missense mutations, which more commonly present with PED in older patients. Despite these trends, there remains considerable clinical heterogeneity that is not explained by mutation type alone. The majority of reported patients with PED carry a de-novo heterozygous mutation in *SLC2A1*. About 10% of affected individuals have a clinically affected parent. PED age at onset is variable and ranges from 1 to 50 years, but is usually in childhood. Attacks are choreo-dystonic in nearly all patients and present predominantly focal/unilateral involvement (leg>arm>face), generalization of attacks is unusual. Additional features reported during the attacks can be occasionally seen and include oculogyric crises, gait disturbances, clumsiness, weakness, and migraine. Isolated PED can be seen in up to one–third of cases with

SLC2A1 mutations. Frequency of attacks ranges from several per day to 1 per month. PED can have a positive but partial response to a ketogenic diet. There is remarkable heterogeneity of paroxysmal movement disorders in patients with GLUT1 deficiency syndrome. In one study of patients with GLUT1 deficiency syndrome, non-epileptic paroxysmal events were found in one-third of cases and comprised episodes of ataxia, parkinsonian features, weakness, and PNKD. It has been demonstrated that 'paroxysmal choreoathetosis with spasticity' (formerly associated with the DYT9 locus) is also due to *SLC2A1* mutations.

It should be kept in mind with regard the differential diagnosis, that PED may be a presenting feature of early-onset Parkinson's disease (PD). Also, dopa-responsive dystonia due to mutations in the GTP cyclohydrolase 1 gene (GCH1) can also present as PED. Finally, PED has also been reported to be symptomatic to basal ganglia lesions. Ancillary investigations are therefore necessary including cerebrospinal fluid (CSF) investigations for glucose, lactate, pterins, and dopamine metabolites and possibly dopamine transporter scans in the appropriate context.

Alternating Hemiplegia of Childhood

AHC is a largely sporadic disorder with an estimated prevalence of 1 case in 1 million people and with onset within the first 18 months, by definition. Recently, studies using whole exome sequencing demonstrated heterozygous de novo mutations in the *ATP1A3* gene to be causative of AHC. *ATP1A3* is a neuron-specific p-type Na1/K1-ATPase with particular importance in sodium coupled transport of various molecules, osmoregulation, and excitability of nerves and muscles. Its clear that in AHC frequent episodes of either hemidystonia or hemiplegia can manifest together with other paroxysmal symptoms including nystagmus, anarthria, dysphagia, hypersalivation, and seizures. Duration of attacks ranges from a few minutes to several days, and episodes recur from repeatedly within a day to several times a month. A meta-analysis of genetically proven AHC cases has showed that all patients presented with both hemiplegic and hemidystonic attacks, which here induced by emotional stressors and physical stressors such as temperature changes, respiratory tract infections, and bright lights. Characteristically, there is a rostrocaudal gradient in the hemiplegic/hemidystonic episodes (face/neck>arm>leg). Hemiplegic and hemidystonic episodes typically shift from one side of the body to the other and typically disappear falling asleep. Interestingly, *ATP1A3* gene mutations are not only the primary cause for AHC, but also for rapid-onset dystonia-parkinsonism (RDP). AHC and RDP phenotypes can overlap and many patients show an "intermediate" phenotype, suggesting a continuous spectrum.

EPISODIC ATAXIAS

EA are rare neurological conditions characterized by episodes of incoordination and imbalance, often with associated progressive ataxia. There are at least six different types of EA associated with different genetic loci but only for two of these disorders, EA type 1 (EA1) and type 2 (EA2), the causative gene has been identified to date. The genetic identification of these genes broadened the clinical spectrum of EA, now known to be variably associated with epilepsy, dystonia, hemiplegic migraine, myasthenia and even intermittent coma.

Episodic Ataxia type 1 (EA1)

EA1 is rare autosomal dominant disorder characterized by brief episodes of ataxia lasting seconds to minutes and interictal myokymia. The onset is typically in early childhood and physical and emotional stress, startle or sudden movements trigger the episodes of ataxia often with dysarthria and tremor. The interictal myokymia may be detected either clinically or on electromyography. Although the attack are frequent, occurring up to 30 times a day atypical variants with prolonged attacks lasting 5 to 12 h have also been described. Acetazolamide is effective in reducing attacks frequency in some patients.

EA1 is caused by mutations in the *KCNA1* gene encoding voltage gated potassium channel, which is highly expressed in the cerebellum and perinodally along motor axons.

Episodic Ataxia type 2 (EA2)

EA2 is by far the most common episodic ataxia syndrome [80]. EA2 is characterized by longer episodes of ataxia (hours) than in EA1, with interictal nystagmus and mildly progressive baseline ataxia. As with EA1, onset of EA2 is typically early in life and episodes are commonly triggered by physical and emotional stress. Episodes can vary from a pure ataxia to combinations of symptoms, including vertigo, nausea and vomiting, which are the most commonly associated symptoms and occur in more than half of the patients. During the attacks, patients typically exhibit a spontaneous nystagmus. Between episodes, the most common finding is a gaze-evoked, usually down-beating, nystagmus. The attacks can be dramatically responsive to acetazolamide.

It is worth to note that EA2 is allelic with Familial Hemiplegic Migraine type 1 (FHM1).

The disease locus of EA2 was first mapped to chromosome 19p, as where a calcium channel gene, *CACNA1A*, was also mapped. Ophoff et al. charterized the genomic structure of *CACNA1A* and identified truncation (frameshit and splice site) mutations in EA2 and missense mutations in FHM1 Interestingly, a CAG-repeat expansion in *CACNA1A* causes spinocerebellar ataxia type 6 (SCA6). Hence, EA2, FHM1, and SCA6 are allelic disorders, all caused by mutations in *CACNA1A*.

OTHER GENETICALLY DETERMINED EA's (EA5 AND EA6)
EA5 has been genetically determined when a series of families with EA were screened for mutations in the calcium channel b4 subunit CACNB4, on chromosome 2q. Clinically, EA5 is similar to EA2, with attacks lasting hours and without associated myokymia.

However, response to acetazolamide can be lost over time in EA5. EA6 causes episodic and progressive ataxia with episodes of hemiplegia and epilepsy. A de novo mutation was identified from a screen of the candidate gene SLC1A3, a glutamate transporter localized to astrocytes.

SOME PITFALLS OF CLINICAL CLASSIFICATIONS

The discovery of the genes for the different forms of PxDs using the classification diving Pxd's into the major forms (i.e., PKD, PNKD, and PED) and the corresponding mutations in the *PRRT2*, *MR-1*, and *SLC2A1* genes, respectively. However, although the genotype-phenotype correlations are fairly robust, it has become clear that there is notable overlapping. A number of patients with *PRRT2* mutations clinically also had PNKD and/or PED like episodes, while patients with *MR-1* mutations can present as PED and inversely patients with *SLC2A1* mutations can have PNKD like clinical episodes. In some instances, there is also some overlap between PxD and EA e.g *PRRT2* mutation carriers may present with episodes of ataxia. All these examples are the exception rather than the rule, but they cannot be neglected.

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Table : List of some common secondary forms of PxD

- Demyelination
- Vasculopathy,
- Infectious disease
- Cerebral and peripheral trauma
- Neurodegenerative disease
- Hormonal and metabolic dysfunction:
  Diabetes mellitus, Hyperthyroidism and hypoparathyroidism, pseudohypoparathyroidism,
- Neoplasm
- Chiari malformation, cervical syringomyelia
- Cerebral palsy after perinatal hypoxia
- Drug-induced
- Faciobrachial dystonic seizures (LG1 antibodies