Original Articles

Channelopathy: Hypothesis of a Common Pathophysiologic Mechanism in Different Forms of Paroxysmal Dyskinesia

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Paroxysmal dyskinesias are a rare heterogeneous group of neurologic disorders, characterized by transient sudden choreoathetoid or dystonic attacks without loss of consciousness. This study reports a family with six affected members in three generations, and two sporadic cases of paroxysmal dyskinesia. Familial cases of paroxysmal dyskinesia are affected by idiopathic long-lasting paroxysmal exertion-induced dyskinesia and the sporadic cases by idiopathic short-lasting paroxysmal kinesigenic dyskinesia. Familial cases also suffer from epilepsy, mainly of generalized type, with benign outcome; one sporadic case is affected by migraine. Results presented in this neurophysiologic study include electromyography, somatosensory evoked potentials by median nerve stimulation, somatosensory evoked potentials by posterior tibial nerve stimulation, motor evoked potentials by magnetic transcranial cortical stimulation, visual evoked potentials, brainstem auditory evoked potentials, blink reflex, reflex H, and electroencephalography. The clinical and neurophysiologic findings presented here suggest a condition of hyperexcitability at the muscular and brain level, perhaps as a result of an ion channel disorder, which is in agreement with reports in the literature. © 2005 by Elsevier Inc. All rights reserved.

Introduction

Paroxysmal dyskinesias are a rare group of heterogeneous neurologic disorders, characterized by transient sudden attacks of choreoathetosis or dystonia, without loss of consciousness [1-6]. Various classifications of paroxysmal dyskinesia have been proposed [2,3,7]. Paroxysmal dyskinesias are traditionally divided into paroxysmal kinesigenic dystonia/choreoathetosis and nonkinesigenic paroxysmal dystonic choreoathetosis [2-4]. However, in 1995 Demirkiran and Jankovic proposed a new classification based chiefly on precipitating events, but also on duration of attacks, and etiology [5]. These authors used the generic term *dyskinesia* because it is difficult to specifically determine the type of hyperkinetic movements (dystonic, choreic, choreoathetoid, ballistic). The term broadly correlates with paroxysmal kinesigenic dystonia/choreoathetosis, paroxysmal dystonic choreoathetosis, and the intermediate variety of the old classification. However, the authors further subclassified patients in each category as having either short or long attacks, depending on whether the episode lasted up to 5 minutes or longer. Each case in each subcategory was also classified as either idiopathic (familial/sporadic) or secondary, depending on the etiology. A recent genetic classification of the dystonic syndromes identified three genetic loci for paroxysmal dyskinesia, DYT8, DYT9, and DYT10 [8], yet the cause of this condition remains uncertain.

This study describes a family (with six affected members in three generations) and two sporadic cases of paroxysmal dyskinesia. Clinical and diagnostic evaluation of these patients suggests an ion channel disorder. The familial cases were affected by idiopathic long-lasting

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paroxysmal exertion-induced dyskinesia, and the sporadic cases were affected by idiopathic short-lasting paroxysmal kinesigenic dyskinesia. The familial cases also suffered from epilepsy, mental retardation, and impulsivity. One sporadic case is affected by migraine.

Case Reports

Familial Cases (Paroxysmal Exertion-induced Dyskinesia)

Six members of a family, in three generations, presented with a syndrome characterized by idiopathic long-lasting paroxysmal exertion-induced dyskinesia, epilepsy, mental retardation, and behavioral disorders. This family has been previously described [9-11]. The dyskinesia attacks appeared in childhood and were characterized by dystonia and choreoathetosis, with flexion and extension, and by alternate twisting of upper and lower limbs. Two patients also experienced oro-buccal movements. The dyskinesias were induced by prolonged exercise or fasting; they usually lasted 10 to 40 minutes, with weekly frequency. All patients also had epilepsy, with childhood-adolescence onset, mainly of idiopathic generalized type. All patients manifested brisk, deep tendon reflexes and cognitive impairment. Impulsivity, irritability, hyperactivity, and aggressivity toward property and persons emerged in three members. None of the nonaffected members of this family had either dyskinesia or epileptic manifestations alone.

During 8 years of follow-up, the patients received several antiepileptic drugs (sodium valproate, magnesium valproate, phenobarbital, carbamazepine, phenytoin, ethosuximide, clonazepam, lorazepam, gabapentin), and one patient also received levodopa. The dyskinesias decreased in severity and frequency with carbamazepine in three cases, and with carbamazepine and ethosuximide in one case. One patient manifested variable response to carbamazepine, gabapentin, and levodopa. One patient did not receive any therapy because a dyskinesia attack only appeared at the age of 27 years. In all the subjects, epilepsy had a benign outcome and was well controlled by therapy.

Sporadic Case 1 (Paroxysmal Kinesigenic Dyskinesia)

This patient, a 17.8-year-old male, was born after a term pregnancy. He had perinatal asphyxia. His family history was negative for neurologic and psychiatric disorders. Psychomotor developmental milestones were normal. He displayed a tonic stuttering since the age of 3 years. At the age of 9 years, he developed left fronto-temporal migraines, without aura and with monthly frequency.

At the age of 12.8 years, he presented dystonic and rarely choreoathetoid movements resembling puffing, initially involving the perioral muscles. After some days, the abnormal movements spread to the neck, with repetitive hyperextensions and left latero-versions lasting 2-3 seconds, and were never associated with loss of consciousness. The dyskinesias were induced by sudden movements, such as postural changes, and by fatigue and stress. After 1 month, dyskinetic attacks increased in duration (2-3 minutes) and frequency (several clusters a day) and became more serious, involving the neck, trunk (in hyperextension), and the pharyngo-laryngeal muscles, with emission of guttural sounds and dyspnea.

At our first observation, at the age of 13.7 years, the frequency of the dyskinesias attacks averaged 100/day, obliging the patient to lie in supine position. The patient also manifested tonic stuttering and some mimic tics. Systemic examination gave normal findings except for the occurrence of multiple Sutton's nevi. Neurologic examination revealed increased tendon reflexes and bilaterally absent cutaneous plantar response. Cognitive skills were normal; mental evaluation revealed symptoms of social anxiety, poor initiative in social relations, and difficulty in emotional reciprocity.

Before our observation, the patient received haloperidol and the dyskinesias disappeared temporarily. Under our observation, levodopa 125 mg daily was initiated. After 1 week, the dyskinesias reduced in duration and frequency and then disappeared. During 4 years of follow-up the outcome was variable: in some periods breakthroughs occurred, with variable duration, and levodopa was resumed leading to a reduction of the abnormal movement; after a 2-month period of absence of abnormal movements, levodopa was discontinued. In the last year, the patient was prescribed levodopa (200 mg daily) and magnesium valproate (400 mg daily). Dyskinesia and migraine attacks were reduced in frequency.

Sporadic Case 2 (Paroxysmal Kinesigenic Dyskinesia)

This patient, a 15.9-year-old male, had normal gestation, birth, and early developmental milestones and no apparent neurologic conditions in his family. His medical history was normal, except for an appendectomy at 6 years.

At the age of 12 years, he was referred to our service because he experienced dystonic movements. These movements were characterized by repetitive torsional contractions, involving initially the right hand and successively the right foot and leg; they lasted few seconds, and were sporadic (monthly frequency). After a few months, the episodes increased in frequency, averaging 2 to 10 per day and became generalized. They were characterized by sudden arching and torsion of the trunk and neck, slow abduction of the shoulders with internal rotation of the arms, inversion of the foot with plantar flexion, facial grimaces, and torsion of the tongue, followed by pain. In some instances, the paroxysmal dyskinesias caused unsteadiness and even a fall. The dyskinesias occurred abruptly after a sudden voluntary movement (for example: starting to run, standing up from a chair, jumping up to answer a ringing telephone or starting to walk at a traffic light) but could also be induced by being startled and by emotional stress and anxiety. The dyskinesias were either athetosis or dystonia and rarely ballism. Sometimes a tingling or a strange sensation of the right leg occurred before the dyskinesia attack, or the tingling occurred without a subsequent attack. The patient did not lose consciousness and had no neurovegetative manifestations during the episodes. He was able to stop the beginning of an attack by assuming some postures; afterwards he could recall what happened, but speech was affected during the episode.

A general examination revealed a nevocellular nevus, an epidermal nevus, and atrial extrasystole. The neurologic examination revealed only increased tendon reflexes; cognitive skills were normal. Psychic evaluation evidenced aspects of social anxiety, poor interest and poor initiative in social relations, and difficulty in emotional reciprocity.

The follow-up continued for 2,2 years. Under our observation, gabapentin 600 mg/day was initiated and was continued for 15 months, during which the dyskinesias reduced in severity and frequency (1/week), increasing only during periods of scholastic stress. In the last 11 months, the patient did not receive therapy and manifested only sporadic sensations of movement.

Diagnostic Evaluation

The diagnostic assays performed are listed in Table 1.

All general, endocrinologic, and metabolic investigations were normal, except for antinuclear antibodies that were increased (titer: 1/320; normal valve (n.v.): 1/40) in the sporadic case 1. Electrocardiogram and Holter-electrocardiogram of sporadic case 2 documented arrhythmia with atrial escape. Preliminary genetic screening for homozygosity in the probands of chromosome 16 for familial cases was negative (unpublished observations of Dr. G. Casari, TIGEM, Milan, Italy). A genetic study for dopa-sensitive dystonia was negative in the sporadic case 1.

Six cases (four familial cases and both sporadic cases) were submitted to a neurophysiologic study which included electromyography, somatosensory evoked potentials by median nerve stimulation, somatosensory evoked potentials by posterior tibial nerve stimulation, motor evoked

Table 1. Diagnostic investigations

General investigations (complete blood count, serum total protein and electrophoresis, hepatic and renal function tests, glucose, immunoglobulins, complement system, prothrombin and partial thromboplastin times, serum and urinary electrolytes, serum calcium and calcium ion, lactic dehydrogenase, creatine kinase, alkaline phosphatase, serum copper, urine copper, ceruloplasmin, urinary vanillylmandelic acid, erythrocyte sedimentation rate, antistreptolysin-O titer, rheumatoid factor, TORCH titers)

Endocrinologic investigations (serum insulin, calcitonin, parathormone, thyroid function, cortisol, adrenocorticotropic hormone)

Metabolic investigations (serum lactate, pyruvate, arylisulfatase A and B, vitamin E, carnitine, very long chain fatty acids, ammonemia, aminoacidemia, and aminoaciduria)

Autoantibodies

Magnetic nuclear resonance imaging of brain (three familial cases and both sporadic cases)

Spectroscopic magnetic nuclear resonance studies (sporadic case 2)

Ophthalmologic examination (also with slit-lamp examination)

Cardiac visit, ECG, Holter-ECG

Echography of abdomen

Abbreviations:
ECG = Electrocardiogram
TORCH = Toxoplasmosis, others, rubella, cytomegalovirus, and herpes simplex virus

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potentials by magnetic transcranial cortical stimulation, visual evoked potentials, brainstem auditory evoked potentials, blink reflex, reflex H, and electroencephalography (Table 2). Evoked potentials were considered abnormal when values were more than 2.5 S.D. above the mean of a sex-age-height matched control group of 20 healthy subjects.

Visual evoked potentials, brainstem auditory evoked potentials, blink reflex, and reflex H were normal.

Electromyographic examination, in muscular rest condition, revealed spontaneous activity characterized by doublets and triplets in five patients. Myotonic discharges were recorded only in one familial case. For somatosensory evoked potentials by median nerve stimulation, latency and morphology of N9 (Erb's point potential), N13 (cervical potential), N20-P25 (parietal complex), P22-N30 (frontal complex), N20/P25 and P22/N30 peak-to-peak amplitudes and the central conduction time (calculated as N20 and N13 latencies difference) were analyzed. For somatosensory evoked potentials by posterior tibial nerve stimulation, latency and morphology of L3 spine potential, P37 and N45 (parietal components) and conduction time cauda equina scalp (computed by subtracting the latency of the L3 spine potential from the latency of the P37 parietal potential) were studied. Somatosensory evoked potentials by median nerve stimulation and somatosensory evoked potentials by posterior tibial nerve stimulation disclosed bilateral normal latency of main waves (N9, N13, N20, N30) and normal central conduction time. In all cases, the amplitude of cortical components (parietal N20-P25 complex and frontal P22-N30 complex) for median nerve stimulation was bilaterally reduced, with inversion of the N20/N30 ratio. In five cases, the amplitude of cortical components (P37-N45 complex) for posterior tibial nerve stimulation was bilaterally reduced. In one case, light morphologic abnormalities of parietal cortical components for right posterior tibial nerve stimulation were recorded.

The intensity level of magnetic transcranial cortical stimulation was 10% above threshold. Motor evoked potentials were recorded over the abductor brevis pollicis, at rest and during motor facilitation at maximum voluntary contraction. In five cases, motor evoked potentials by magnetic transcranial cortical stimulation produced a lowered threshold and an increased amplitude. These findings were associated with potentiation of the motor facilitation during muscular contraction in all patients, during mental activity (calculation) in both sporadic cases, and during the thought of emotive stress in sporadic case 2.

These neurophysiologic evidences suggest a condition of hyperexcitability at the muscular and brain level.

Discussion

According to Demirkiran and Jankovic's classification [5], familial cases are affected by idiopathic long-lasting paroxysmal exertion-induced dyskinesia and sporadic cases by idiopathic short-lasting paroxysmal kinesigenic dyskinesia.

Paroxysmal exertion-induced dyskinesia is a rare movement disorder. Only 16 cases reported in the literature are sporadic, the other are familial [2,5,9-21]. Associations between paroxysmal exertion-induced dyskinesia and epilepsy [9-11,16,18,20], paroxysmal exertion-induced dyskinesia and hemiplegic migraine [19], and paroxysmal exertion-induced dyskinesia and rolandic epilepsy with writer's cramp (RE-PED-WC) [18] have been reported.

Paroxysmal kinesigenic dyskinesia involves sudden attacks of involuntary movements, including dystonic postures, chorea, athetosis, or ballism, precipitated by sudden movement. However, startling occurrences, hyperventilation, and continuous exercise can also trigger episodes [12]. Co-occurrence of paroxysmal kinesigenic dyskinesia and epilepsy or paroxysmal kinesigenic dyskinesia and benign infantile convulsions in the same individual or their familial aggregation is frequent [20-26]. A homogeneous autosomal dominant syndrome of infantile convulsions (from 3 to 12 months) and paroxysmal nonkinesigenic dyskinesia (onset later) has been described (ICCA) [27,28]. In addition, Singh et al. [29] reported a family with association between paroxysmal kinesigenic dyskinesia, febrile seizures, febrile seizures plus, migraine, and hemiplegic migraine.

Most cases of paroxysmal dyskinesia are primary, categorized as familial (usually autosomal dominant) or idiopathic. However, in some cases a specific cause of paroxysmal dyskinesia has been identified [30]. The cases of paroxysmal kinesigenic dyskinesia reported in literature are heterogeneous in types and localization of abnormal movements, and precipitating factors also in the same family, thus it is hypothesized that multiple factors cause the phenotype. The presence and the type of epilepsy can vary between families and within the same family.

In the cases reported here, the phenotype of the sporadic cases is not homogeneous. The phenotype of familial cases is more complex because the dyskinesias are associated with epilepsy, mental retardation, and impulsivity; the clinical expression of dyskinesias is quite homogeneous, whereas epilepsy is manifested in different forms and at different ages, even if it is mainly of a generalized type.

Clinical and pharmacologic reports suggest that paroxysmal kinesigenic dyskinesia and paroxysmal exertion-induced dyskinesia have different pathophysiologies. Abundant uncertainties persist regarding the pathophysiologic and anatomic bases of paroxysmal dyskinesia and of dystonia.

Table 2. Neurophysiologic findings in four familial cases and in both sporadic cases

Case	EMG	MN-SEPs	PTN-SEPs	MEPs	EEG
FC 1	Myotonic discharges Doublet and triplet discharges	↓ Amplitude of parietal and frontal cortical components bilaterally	↓ Amplitude of parietal and frontal cortical components bilaterally	↓ Threshold ↑ Amplitude ↑ Motor facilitation	Bursts of generalized 3–3.5 Hz spike-wave complexes → normal
FC 2	Doublet and triplet discharges	↓ Amplitude of parietal and frontal cortical components bilaterally	↓ Amplitude of parietal and frontal cortical components bilaterally	↓ Threshold ↑ Amplitude ↑ Motor facilitation	Bursts of generalized 3–3.5 Hz spike-wave complexes → normal
FC 3	Doublet and triplet discharges	↓ Amplitude of parietal cortical components for the right median nerve stimulation and amplitude reduction of frontal components bilaterally	Slight morphologic abnormalities of parietal cortical components for right PTN stimulation	↓ Threshold ↑ Amplitude ↑ Motor facilitation	Focal spikes over left temporo-central regions
FC 4	Normal	↓ Amplitude of N 9 and frontal components bilaterally	↓ Amplitude of parietal cortical components bilaterally	Not performed	Atypical single spike-wave complexes over right or left temporo-occipital regions
SC 1	Doublet and triplet discharges	↓ Amplitude of parietal and frontal cortical components bilaterally	↓ Amplitude of parietal cortical components bilaterally	↓ Threshold ↓ Amplitude ↑ Motor facilitation	Aspecific slow anomalies over left temporo-central regions
SC 2	Doublet and triplet discharges	↓ Amplitude of parietal and frontal cortical components bilaterally	↓ Amplitude of parietal cortical components bilaterally	↓ Threshold ↑ Amplitude ↑ Motor facilitation	Excess of theta in left hemisphere

Abbreviations:
EEG   = Electroencephalography
EMG   = Electromyography
FC   = Familial case
MEPs   = Motor evoked potentials by magnetic transcranial cortical stimulation
MN-SEPs = Somatosensory evoked potentials by median nerve stimulation
PTN-SEPs = Somatosensory evoked potentials by posterior tibial nerve stimulation
SC   = Sporadic case

Some authors consider paroxysmal dyskinesia to be a subcortical epilepsy involving thalamus or basal ganglia [22,31]. Investigation of spinal and brainstem reflexes (blink reflex, H reflex) suggests that inhibitory processes are reduced, thus a dysfunction of spinal and brainstem motor modulation is hypothesized [32-34]. On the other hand, clinical and neurophysiologic evidence suggests that abnormalities of the somatosensory system may contribute to paroxysmal dyskinesia: an impaired inhibition of the somatosensory system at spinal and cortical levels would lead to an abnormal sensory connection to ongoing motor programs, ultimately resulting in the motor abnormalities present in this disease; the fundamental disturbance would be an abnormal supraspinal command signal rather than disordered spinal circuitry [33,35-37]. On the other hand, there are numerous demonstrations of defined abnormalities of the cortical motor system (motor evoked potentials, transcranial magnetic stimulation, double pulse paradigm) such as increased excitability of the motor cortex due to increased motor evoked potential amplitudes, increased motor facilitation, increased motor evoked potential map size, decreased inhibition, and shortened silent period [35].

Two other hypotheses in the literature suggest that anomalies of basal ganglia or mutations in central nervous system ion channels may cause paroxysmal dyskinesia.

Basal ganglia dysfunction cannot be excluded because of the clinical features of the abnormal movements, the presence of symptomatic paroxysmal kinesigenic dyskinesia in specific lesions of basal ganglia, and the findings of magnetic resonance spectroscopy and positron emission tomography studies [38-40]. The multiple manifestations of movement disorders, with differing etiologies, may share a common, generic mechanism in terms of basal ganglia output. Clinical, experimental, and pharmacologic evidence demonstrates that an over-activity of the striatonigral direct pathway (with the function to inhibit output from basal ganglia), and an under-activity of the striatopallidal indirect pathway (with the function to activate output from basal ganglia) could lead to excessive activation of the cortex, mediated by thalamic disinhibition (abnormally reduced activity in the thalamic afferents from the basal ganglia, the majority of which originate from the medial segment of the globus pallidus) [40]. In our cases, the hypothesis of dysfunctional basal ganglia

cannot be excluded because of the symptomatogy of the abnormal movements and the good response to levodopa in two patients and to gabapentin (antiepileptic that enhances γ-aminobutyric acid transmission) in three patients. However, others facts did not emerge to sustain this hypothesis.

A channelopathy for paroxysmal dyskinesias could be considered, for the followed reasons. Clinically, paroxysmal dyskinesias display common features with other paroxysmal central nervous system disorders considered to be disorders of ion channels, thus suggesting a common pathophysiologic mechanism [41-46]: episodic attacks on a normal interictal background and similar precipitating factors (such as stress, fatigue, and diet), overlap with regard to drug treatment (carbamazepine is useful for epilepsy and paroxysmal kinesigenic dyskinesia, acetazolamide is useful for periodic paralysis, myotonia, episodic ataxia, and some paroxysmal dyskinesias). Moreover, all these paroxysmal disorders exhibit analogies and associations between them, also in the same family [7,9-11,16,19-29].

In our familial and sporadic patients affected by different forms of paroxysmal dyskinesia, neurophysiologic findings, similar phenotype aspects, and responses to antiepileptic drugs support the hypothesis of a channelopathy. The neurophysiologic studies suggest a condition of hyperexcitability at the muscular and brain membrane levels in all patients. The reduction in amplitude of somatosensory evoked potentials recorded in all patients, even during apparent complete relaxation, could be explained with a proprioceptive interference on the sensory evoked inputs by the neuromuscular hyperexcitability. In all patients, corticomotor evoked potentials revealed decreased motor threshold, increased amplitude, and potentiation of motor facilitation during muscular contraction, during mental activity in both sporadic cases and during emotional stress in sporadic case 2. These motor evoked potentials findings might be explained by enhancement of spinal excitability related to proprioceptive inputs. The same mechanism might give rise to the brisk deep tendon reflexes observed in all patients.

Paroxysmal dyskinesia in the patients described in the present study coexists with epilepsy in familial cases and with migraine in sporadic case 1. In sporadic case 2, also cardiac membrane instability was manifested with atrial extrasystole. In accordance with literature reports, the co-occurrence of paroxysmal dyskinesia and age-dependent epilepsy in familial cases, and of paroxysmal dyskinesia and migraine in sporadic case 1, could be the polymorphic expression of a condition of hyperexcitability: a mutation of an ion channel could cause an abnormal excitability in the cortical cortex and basal ganglia at different ages, with age-dependent expression of different subunits of multisubunit ion channels or by different grades of function of the same subunit in several neuroanatomic systems [47].

Finally, in some patients, antiepileptic drugs that affect ion channels resulted in improvement of dyskinesias.

In accordance with the literature, the heterogeneity of the forms of paroxysmal dyskinesia in the cases reported here does not exclude the hypothesis that mutations in ion channels may cause paroxysmal dyskinesia. In fact, it is known that, in channelopathies, mutations in some ion channels can give different phenotypes in relation to the localization of the pathologic channel [44]. According to the location-selectivity principle, the anatomic location of a specific channel type determines its function (for example, nicotinic acetylcholine receptor channels in the frontal lobe are structurally and functionally different from nicotinic acetylcholine receptor channels at the neuromuscular junction) [43]. Moreover, a dysfunction of different ion channels can result in similar clinical phenotypes because of the principle of channel interdependency in which the normal excitability of neuronal and muscle membranes requires the integrated function of many ion channels [43]. Finally, according to the genetic heterogeneity principle, some functions may be regulated by more than one gene, thus different genetic mutations may result in the same pathologic phenotype (for example, congenital myasthenic syndromes may be caused by 56 different mutations that cause a dysfunction of the neuromuscular junction) [43].

Genetic studies also support the hypothesis of a channelopathy for paroxysmal dyskinesia [41-46,48-55]. The genetic loci of some paroxysmal dyskinesias (paroxysmal nonkinesigenic dyskinesia and paroxysmal choreoathetosis and episodic ataxia and spasticity [CSA]) are located on chromosomes that have clusters of ion channel genes (i.e., the sodium ion channel gene is on chromosomes 1 and 2) [50-52]. Recently, two separate loci of paroxysmal kinesigenic dyskinesia (EKD1 and EKD2) have been mapped to chromosome 16 in families from various ethnic backgrounds, overlapping the locus of ICCA and REPED-WC, and a third locus (EKD3) cannot be excluded [53-55]. To date, the genes encoding or controlling ion channel function have not been identified within the candidate regions on this chromosome, but it is possible that genes currently of unknown function may later prove to be ion channel genes or that membrane stability is disrupted by some other mechanism [55]. An investigation of the GeneMap '99 Database revealed that in the pericentromeric region of chromosome 16, on interval ICCA and paroxysmal kinesigenic dyskinesia, a cluster of genes exist that code for co-transporters and genes involved in the modulation of membrane excitability via signal transduction.

In our patients affected by different forms of paroxysmal dyskinesia, it is possible to hypothesize that different mutations in ion channels may result in a similar phenotype of involuntary movements, but in different phenotypes for precipitating factors and response to therapy. Advances in genetic studies, in particular molecular analysis, may help explain the pathophysiology to formulate better classification of paroxysmal dyskinesias, which is

currently based only on clinical criteria. These studies may also help identify more rational therapy for this disorder.

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