Movement disorders

Paroxysmal movement disorders: An update

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ABSTRACT

Paroxysmal movement disorders comprise both paroxysmal dyskinesia, characterized by attacks of dystonic and/or choreic movements, and episodic ataxia, defined by attacks of cerebellar ataxia. They may be primary (familial or sporadic) or secondary to an underlying cause. They can be classified according to their phenomenology (kinesigenic, non-kinesigenic or exercise-induced) or their genetic cause. The main genes involved in primary paroxysmal movement disorders include PRRT2, PNKD, SLC2A1, ATP1A3, GCH1, PARK2, ADCY5, CACNA1A and KCNA1. Many cases remain genetically undiagnosed, thereby suggesting that additional culprit genes remain to be discovered. The present report is a general overview that aims to help clinicians diagnose and treat patients with paroxysmal movement disorders.

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Paroxysmal neurological disorders are characterized by episodes of neurological dysfunction that are either isolated or part of a more complex disorder with ictal manifestations. They encompass apparently heterogeneous disorders such as migraine, epilepsy, periodic paralysis and paroxysmal movement disorders. They are, however, all linked by a common pathophysiological feature, namely neuronal hyperexcitability, and by overlapping genetic causes.

Paroxysmal movement disorders are rare disorders that can be divided into paroxysmal dyskinesias (PxDs) and episodic ataxias (EAs). PxDs are characterized by attacks of dystonic and/or choreic movements, whereas EAs are defined by attacks of cerebellar ataxia. They may be primary (mostly of genetic origin) or secondary to underlying causes, such as lesions of the central nervous system or metabolic disorders. Primary PxDs may be familial or sporadic, with onset in either childhood or adolescence.

A new classification is emerging, based on both clinical and genetic characteristics [1]. Indeed, recent genetic advances are rendering the historical, clinically based classification obsolete: a given paroxysmal movement disorder can be caused by mutations in various genes, while mutations in a given gene can give rise to various paroxysmal disorders. The present review provides an update on the clinical characteristics, genetic causes and pathophysiology of paroxysmal movement disorders.

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1. Clinical characteristics and phenomenological classification

The first step in the diagnostic process is to determine whether the disorder is likely to be primary or secondary. Signs of an underlying cause include onset in adulthood, the absence of a family history, variable duration of attacks and triggering factors, abnormal interictal clinical status, and abnormal laboratory or magnetic resonance imaging (MRI) findings. Clinical classification is based on the phenomenology, triggering factors and duration of attacks; a diagnostic algorithm can provide some guidance (Fig. 1). However, some patients may have paroxysmal movement disorders that do not fall into any of the proposed categories, and paroxysmal events corresponding to more than one category may be present in a given case.

1.1. Paroxysmal kinesigenic dyskinesia

Paroxysmal kinesigenic dyskinesia (PKD) is characterized by attacks of dystonia and/or chorea triggered by sudden voluntary movement and lasting from a few seconds to a minute (see Box 1) [2]. PKD is the most frequent form of PxD, albeit with an estimated prevalence of only 1:150,000 [3]. Onset is usually in childhood or adolescence, with a reported range...
of 6 months to 33 years [4]. There is a male predominance in sporadic cases (gender ratio of 3–4 to 1), but not in familial cases [4].

Attacks may be triggered by sudden initiation of movement, such as getting up from a seated position, or by modification of an ongoing movement, such as breaking into a run while walking. These attacks are favored by stress, and may also be induced by startling or sound or light stimulation. Most patients experience auras such as tingling sensations or general unease, which may sometimes allow them to control the attacks [2,4,5]. The attacks may be focal, multifocal or generalized, and can involve the limbs, trunk and/or speech (through orofacial involvement). There is no pain or loss of consciousness during attacks. The frequency of attacks is variable, ranging from < 1 per month to up to 100 per day. They usually wane or even abate during adulthood. In primary pure PKD, interictal examination is normal. Migraine or epilepsy may be present, especially benign infantile epilepsy, forming part of the infantile convulsions and choreoathetosis (ICCA) syndrome [6]. Treatment with low doses of antiepileptic drugs, especially those that modulate voltage-gated sodium channels, can suppress or dramatically reduce attacks.

Mutations in the PRRT2 gene are the main cause of isolated PKD [7–11], accounting for 27% to 65% of cases [11–20]. The existence of at least a second culprit gene is suspected in primary PKD [21–24]. The ICCA syndrome might also be due to a mutation in SCN8A [25], although the typical SCN8A-mutated phenotype is one of severe epileptic encephalopathy [26]. ADCY5 mutations cause PKD associated with other PxDs and interictal manifestations [27]. Mutations in the SLC16A2 (MCT8) gene, which codes for a thyroid hormone transporter, may also cause PKD as part of a complex phenotype associating cognitive disability and motor disorders [28,29].

1.2. Paroxysmal non-kinesigenic dyskinesia

Paroxysmal non-kinesigenic dyskinesia (PNKD) is characterized by attacks of dystonia and/or chorea with no clear immediate trigger, lasting for a few minutes to a few hours (see Box 2) [30]. Precipitating factors include coffee, alcohol and stress, whereas attacks may be alleviated by sleep. The attacks are infrequent (rarely > 1 per day), and attack-free intervals may last for months. As in PKD, the attacks tend to diminish with advancing age. Auras resembling those seen in PKD may occur. In primary pure PNKD, interictal examination is normal. PNKD can occasionally be severe or even fatal in cases of laryngeal dystonia causing respiratory failure [31]. Antiepileptic drugs, except for benzodiazepines, are usually ineffective. Some patients have improved with acetazolamide, valproate or levetiracetam [32–34]. Deep brain stimulation can also be helpful in severe or refractory PNKD [35,36].

The main causative gene in PNKD is PNKD (formerly MR-1) [37,38], although it is occasionally due to mutations in PRRT2, sometimes in association with PKD [15,39]. As part of a more complex phenotype, PNKD can be associated with mutations in SLC2A1 [40–45], ATP1A3 [46–49], ADCY5 [27], KCNMA1 [50,51] or in genes encoding the branched-chain α-ketoacid dehydrogenase complex (maple syrup urine disease) [52,53].

1.3. Paroxysmal exercise-induced dyskinesia

Paroxysmal exercise-induced dyskinesia (PED) is characterized by attacks of dystonia and/or chorea triggered by prolonged exercise, typically lasting for 5 to 30 min [4] (see Box 3). The attacks often start in the body part involved in the exercise. The frequency of attacks is variable, depending on the routine level of physical exercise. Symptomatic treatment with antiepileptics, levodopa or acetazolamide is sometimes effective, but usually disappointing [4]. Specific treatment of an underlying disorder may be beneficial.

Mutations in SLC2A1 are the main cause of PED, which can be isolated or part of a more complex phenotype [41,43,44,54–58]. Mutations in GCH1, PARK2 (encoding parkin) or other genes involved in recessive juvenile Parkinson’s disease can occasionally cause PED [4,59–66]. Rare genetic causes include mutations in PRRT2 [15,67,68], ATP1A3 [46–48], ADCY5 [27], PDHA1 and PDHX (pyruvate dehydrogenase deficiency) [69,70].

1.4. Paroxysmal hypnogenic dyskinesia

Paroxysmal hypnogenic dyskinesia (PHD) is characterized by violent attacks of dystonic and tonic movements that occur during sleep and last for around 45 sec. In fact, PHD is almost always a form of frontal lobe epilepsy called ‘autosomal-dominant nocturnal frontal lobe epilepsy’ (ADNFLE) [71]. Mutations have been found in CHRNA4, CHRNA2 and CHRN82,
which code for acetylcholine receptor subunits [72]. Antiepileptic drugs are effective.

1.5. Episodic ataxias

EAs are characterized by attacks of cerebellar ataxia that can last from a few seconds to several days, depending on the underlying cause (Box 4). Attacks may be accompanied by dysarthria, tremor, vertigo, nausea, diplopia, dystonia, hemiplegia, headache, and tinnitus [73–75]. Triggering factors include physical and psychological stress, startle, sudden movements, fatigue, caffeine, alcohol, fever and heat [75]. Intercital examination may be normal, or show nystagmus, cerebellar ataxia, myokymia or dystonia. Cognitive disability and psychiatric disorders may also be present. Onset is usually in childhood or adolescence, and the frequency of attacks ranges from a few per year to several per day. Acetazolamide can reduce the severity and frequency of attacks in some patients. Brain MRI can be normal or show cerebellar atrophy.

The two most common types of EA are caused by mutations in the KCNA1 (EA1) and CACNA1A (EA2) genes. Other genetic causes of EAs include mutations in CACNB4 (EAS) [76] and SLC2A1 (EA6) [77]. However, the genes corresponding to the EA3, EA4, EA7 and EA8 loci are still unknown [78–82]. Rare causes of EAs include mutations in SCN2A [83], FGF14 [84,85], PRRT2 [21,86], SLC2A1 [44,45,87], ATP1A3 [49], PDHA1, PDHX [69] and genes encoding the branched-chain α-ketoacid dehydrogenase complex (maple syrup urine disease) [52].

2. Genetic characteristics and pathophysiology

Most primary paroxysmal movement disorders are of genetic origin even in cases without a family history, as de novo mutations are not uncommon. The main genetic defects are summarized in Table 1, along with the principal characteristics of the corresponding disorders. The first genes to consider in paroxysmal dyskinesia are PRRT2, PNKD and SLC2A1, respectively responsible for most PKD, PNKD and PED cases. It should also be noted that PRRT2 and PNKD mutations induce pure phenotypes of PxD, whereas mutations in other genes are generally responsible for more complex phenotypes. The main causative genes of EAs are KCNA1 and CACNA1A.

2.1. The PRRT2 gene

Mutations in the PRRT2 gene are the main cause of PKD, ICCA syndrome and benign familial infantile epilepsy (BFIE) [7–11,88]. They can also occasionally cause PNKD, PED, EAs, hemiplegic migraine and other headache disorders, paroxysmal torticolis and various forms of epilepsy [24]. PKD, ICCA or BFIE was diagnosed in 94.7% of 1444 PRRT2-mutated patients, leaving only 5.3% of patients with other diagnoses [39]. Inheritance is autosomal dominant with incomplete penetrance. Biallelic PRRT2 mutations have been reported to cause a severe phenotype that can include various kinds of PxD, prolonged episodes of ataxia and cognitive disability [86,89,90].

PRRT2 normally interacts with synaptosomal-associated protein 25 kDa (SNAP25), a presynaptic protein involved in calcium-dependent neuronal exocytosis [91], but this interaction is perturbed by PRRT2 mutations [92]. PRRT2 is also part of AMPA-type glutamate receptor complexes, in which it is associated with the GRIA1 subunit [93]. PRRT2 likely inhibits glutamate release and hinders GRIA1 trafficking to the cell membrane. PRRT2 loss of function mutations may lead to increased glutamate release and glutamate receptor activity, thereby inducing neuronal hyperexcitability.

2.2. The PNKD gene

Mutations in the PNKD gene (formerly MR-1) are the main cause of primary PNKD. Inheritance is autosomal dominant with near-complete penetrance [30]. Three different mutations of the gene have been found in unrelated families of different ethnicities [34,94]. The phenotype is one of pure PNKD with normal interictal examination, and is very homogeneous in PNKD-mutated patients [3,34,67,95,96].

PNKD codes for a synaptic protein that modulates neurotransmitter release [97,98]. Its mutations may induce abnormal dopamine release in response to precipitating factors such as stress, caffeine and alcohol, through a gain-of-function mechanism [97,98].

2.3. The SLC2A1 gene

SLC2A1 codes for glucose transporter 1 (GLUT1), a membrane protein that mediates glucose transport across the blood-brain barrier. Mutations in SLC2A1 cause GLUT1 deficiency, a treatable disease characterized by reduced availability of brain glucose causing a cerebral energy deficit. Sporadic cases, due to de novo mutations, are most common, although familial cases with autosomal dominant inheritance also occur. Rare cases of recessive inheritance have also been reported [99]. The phenotypic spectrum is very wide, ranging from pure PED to severe encephalopathy. Manifestations can include cognitive disability, acquired microcephaly, dystonia, chorea, ataxia, spasticity and paroxysmal manifestations, including seizures and PxDs [44,45,54,55,100–102]. There are no firm genotype–phenotype correlations, although milder forms are often associated with missense mutations resulting in 50–75% residual GLUT1 function, whereas severe forms are usually due to mutations resulting in a 50% loss of GLUT1 [55,102].

Mutations in SLC2A1 are likely to be the main cause of PED [54,56,103], but can also be responsible for PNKD and EAs [44,45,87]. Attacks are most often precipitated by exercise or...
<table>
<thead>
<tr>
<th>Gene</th>
<th>Paroxysmal MD</th>
<th>Age of onset</th>
<th>Attack duration</th>
<th>Other paroxysmal disorders</th>
<th>Interictal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRRT2</td>
<td>PKD/ICCA/PNKD/PED/EA</td>
<td>Childhood-adolescence</td>
<td>&lt; 1 min</td>
<td>BFIS/FS/CAM</td>
<td>None (heterozygous mutations)</td>
</tr>
<tr>
<td>PNKD</td>
<td>PNKD/PED/EA</td>
<td>Childhood-adolescence</td>
<td>Minutes to hours</td>
<td>Epilepsy/Migraine/Paroxysmal sleep disturbances</td>
<td>None (heterozygous mutations)</td>
</tr>
<tr>
<td>SLC2A1</td>
<td>PNKD/PED/EA</td>
<td>Infancy-childhood</td>
<td>Minutes to hours</td>
<td>Epilepsy/Paroxysmal eye movements</td>
<td>Cognitive deficiency</td>
</tr>
<tr>
<td>ATP1A3</td>
<td>PNKD/PED/EA</td>
<td>Infancy</td>
<td>Minutes to days</td>
<td>Epilepsy</td>
<td>Cephalic</td>
</tr>
<tr>
<td>ADCY5</td>
<td>PKD/PNKD/PED/Nocturnal PxD</td>
<td>Infancy-childhood</td>
<td>Minutes to hours</td>
<td>Epilepsy/Dystonia/Chorea</td>
<td>Hypertonia</td>
</tr>
<tr>
<td>GCH1</td>
<td>PED</td>
<td>Infancy-childhood</td>
<td>Minutes to hours</td>
<td>Flaccid attacks</td>
<td>Ataxia</td>
</tr>
<tr>
<td>PANK2</td>
<td>PED/PDHX, DLAT</td>
<td>Adolescence-adulthood</td>
<td>Minutes to hours</td>
<td>Epilepsy</td>
<td>Ataxia</td>
</tr>
<tr>
<td>KCNA1</td>
<td>EA</td>
<td>Childhood-adolescence</td>
<td>Seconds to minutes</td>
<td>Epilepsy/Paroxysmal dyspnea</td>
<td>Myokymia</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>EA</td>
<td>Childhood-adolescence</td>
<td>Hours to days</td>
<td>Migraine/Absence epilepsy/Fluctuating weakness</td>
<td>Mild cerebellar syndrome/Neocortical syndromes</td>
</tr>
<tr>
<td>CACNB4</td>
<td>EA</td>
<td>Childhood-adolescence</td>
<td>Hours to days</td>
<td>Juvenile myoclonic epilepsy/Generalized epilepsy</td>
<td>Nystagmus</td>
</tr>
<tr>
<td>SLC1A3</td>
<td>EA</td>
<td>Childhood-adolescence</td>
<td>Hours to days</td>
<td>Epilepsy/Migraine/Flaccid attacks</td>
<td>Mild cerebellar syndrome</td>
</tr>
<tr>
<td>SCN2A</td>
<td>EA</td>
<td>Childhood</td>
<td>Minutes to hours</td>
<td>Neonatal epilepsy/Paroxysmal pain</td>
<td>None</td>
</tr>
<tr>
<td>FGF14</td>
<td>EA</td>
<td>Childhood-adulthood</td>
<td>Minutes to days</td>
<td>Paroxysmal dystonia/Headaches</td>
<td>Mild cerebellar syndrome</td>
</tr>
<tr>
<td>KCNMA1</td>
<td>PNKD/PKD</td>
<td>Childhood</td>
<td>Seconds to minutes &lt; 1 min</td>
<td>Epilepsy</td>
<td>None</td>
</tr>
<tr>
<td>SLC16A2 (MCT8)</td>
<td></td>
<td>Infancy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 1 (Continued)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Paroxysmal MD</th>
<th>Age of onset</th>
<th>Attack duration</th>
<th>Other paroxysmal disorders</th>
<th>Interictal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN8A</td>
<td>PKD</td>
<td>Infancy–childhood</td>
<td>&lt; 1 min</td>
<td>Epilepsy</td>
<td>Cognitive disability</td>
</tr>
</tbody>
</table>

Italicized symptoms are those rarely associated with mutations in the corresponding gene. PKD: paroxysmal kinesigenic dyskinesia; ICCA: infantile convulsions and choreoathetosis; FNKD: paroxysmal non-kinesigenic dyskinesia; PED: paroxysmal exercise-induced dyskinesia; EA: episodic ataxia; BRSE: benign familial infantile seizures; HM: hemiplegic migraine; FS: febrile seizures; CAE: childhood absence epilepsy.

fasting, whereas carbohydrate intake and rest are alleviating factors. The diagnosis is suggested by a low cerebrospinal fluid (CSF)/serum glucose ratio (< 0.60) and confirmed by genetic analysis. Treatment consists of providing alternative energy supplies to the brain. A ketogenic diet, inducing a switch from glucose to ketone body metabolism, is currently the standard treatment. Adherence is a problem, however, and alternative treatments are therefore needed. Acetazolamide is a possible option, as it was reportedly effective in one case [40]. A dramatic improvement in PxD was recently noted in an open-label pilot trial of triheptanoin, which provides energy substrates to the brain [104], although this needs to be confirmed in a larger controlled study.

2.4. The ATP1A3 gene

Mutations in ATP1A3, which encodes the α3-subunit of the Na⁺/K⁺-ATPase pump, cause rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), the cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS) syndrome [49,105], early infantile epileptic encephalopathy [106] and the relapsing encephalopathy with cerebellar ataxia (RECA) syndrome [107]. AHC is characterized by episodic hemiplegia, dystonic or tonic attacks, cognitive disability and permanent movement disorders. RDP is characterized by rapid onset of dystonia (hours to weeks) and parkinsonism. Paroxysmal dystonia (PND and/or PEd) is reported in most AHC patients, and also in a few RDP patients, either as part of a complex phenotype or as the main symptom [46,48,49,108,109]. The phenotypes overlap, implying that ATP1A3-related disorders may rather be seen as a continuous phenotypic spectrum [107]. ATP1A3 mutation analysis should be considered when a patient presents with paroxysmal episodes of ataxia, hemiplegia or dystonia, with or without interictal manifestations [49].

The Na⁺/K⁺-ATPase pump exchanges Na⁺ for K⁺ through ATP hydrolysis and is therefore a major determinant of resting membrane potentials. In the brain, the α3-subunit (encoded by ATP1A3) is exclusively expressed in neurons, particularly GABAergic neurons of the basal ganglia and cerebellum [110]. Nevertheless, the pathophysiology remains poorly understood, and the observed phenotypic variability is not fully explained by genotype–phenotype correlations [49].

2.5. The GCH1 gene

Heterozygous mutations in the GTP-cyclohydrolase-1 (GCH1) gene cause dopa-responsive dystonia (DRD, or DYTS). They also occasionally cause PED, either in isolation or as part of a more complex phenotype [59]. DRD usually manifests as childhood-onset dystonia with motor fluctuations. Accurate diagnosis is important, as treatment with low-dose levodopa greatly alleviates symptoms; thus, although DRD is probably a rare cause of PED, it is essential to consider a levodopa trial in PED patients.

GCH1 codes for GTP-cyclohydrolase 1, an enzyme that catalyzes the first step in the synthesis of tetrahydrobiopterin, which is essential for dopamine synthesis. GCH1 mutations result in haploinsufficiency with reduced striatal dopamine levels. No genotype–phenotype correlations have been established [111].

2.6. The ADCYS gene

Mutations in ADCYS cause a childhood-onset mixed hyperkinetic movement disorder, typically without ataxia, marked cognitive disability or seizures [112]. The disorder is either stable or progresses very slowly. Diagnostic clues include axial hypotonia, orofacial myoklonus and marked fluctuations. In addition to baseline movement disorders, many patients have PxDs manifesting as various PxD subtypes, including non-epileptic nocturnal paroxysmal dyskinesia [27]. The presence of various types of PxD and/or nocturnal non-epileptic PxD in a given patient points strongly to an ADCYS-related disorder.

ADCYS codes for adenylyl cyclase type 5, which is strongly expressed in the striatum. This protein interacts with Goolf, which is encoded by GNAL, a gene involved in primary dystonia [113]. ADCYS integrates signals from multiple receptors, including adenosine A2A and D1 and D2 dopamine receptors [114]. The pathophysiology likely involves increased adenylyl cyclase activity, thereby affecting signal transduction within the striatum [112].

2.7. The KCNA1 gene

Mutations in KCNA1 cause episodic ataxia type 1 (EA1) [115]. Inheritance is autosomal dominant with incomplete penetrance. Onset usually occurs in childhood or early adolescence. The attacks are brief (seconds to minutes), with a
## Table 2 – Causes of secondary paroxysmal movement disorders (MD).

<table>
<thead>
<tr>
<th>Cause</th>
<th>Paroxysmal MD</th>
<th>Clinical clues</th>
<th>Laboratory findings</th>
<th>MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis &amp; other demyelinating diseases</td>
<td>PKD, PNKD, EA</td>
<td>Onset in adulthood Baseline neurological defects History of stroke Seizures, headaches (moyamoya)</td>
<td>CSF oligoclonal bands, anti-NMO antibodies NA</td>
<td>CNS demyelinating lesions Basal ganglia, thalamus, subcortical white-matter or midbrain infarction</td>
</tr>
<tr>
<td>Stroke (including moyamoya disease)</td>
<td>PKD, PNKD, EA</td>
<td>Onset in adulthood Baseline neurological defects History of stroke Seizures, headaches (moyamoya)</td>
<td>NA</td>
<td>Arterial stenosis</td>
</tr>
<tr>
<td>Transient cerebral ischemia</td>
<td>PNKD</td>
<td>Onset in adulthood Cardiovascular risk factors</td>
<td>None, or hypocalcemia, hyperphosphoremia and abnormal PTH levels</td>
<td>Symmetrical T2 hypointensity &amp; T1 hyperintensity in basal ganglia</td>
</tr>
<tr>
<td>Basal ganglia calcifications</td>
<td>PKD, PNKD</td>
<td>Onset in adulthood Baseline neurological defects Response to calcium supplementation if hypocalcemic</td>
<td>Hypoglycemia or hyperglycemia Autoantibodies</td>
<td>White-matter &amp; basal ganglia T2 hyperintensities</td>
</tr>
<tr>
<td>Hypo-/hyperglycemia</td>
<td>PNKD</td>
<td>Onset in adulthood History of diabetes Systemic involvement</td>
<td>Autoantibodies</td>
<td>Normal or basal ganglia T2 hyperintensities</td>
</tr>
<tr>
<td>Autoimmune encephalopathy (VGKC, Hashimoto)</td>
<td>PKD</td>
<td>Onset in adulthood Cognitive impairment Seizures</td>
<td>Anti-streptolysin O, streptococi in throat culture</td>
<td>NA</td>
</tr>
<tr>
<td>Poststreptococcal disorder</td>
<td>PNKD</td>
<td>Recent upper respiratory tract infection Behavioral changes</td>
<td>Paraneoplastic antibodies</td>
<td>NA</td>
</tr>
<tr>
<td>Paraneoplastic limbic encephalitis</td>
<td>EA</td>
<td>Onset in adulthood Seizures Behavioral changes</td>
<td>NA</td>
<td>Temporal lobe T2 hyperintensity</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>PKD, PNKD</td>
<td>Gastrointestinal disorder Other aura symptoms Attacks followed by migraine Response to migraine treatment</td>
<td>Autoantibodies</td>
<td>NA</td>
</tr>
<tr>
<td>Migraine</td>
<td>PNKD</td>
<td>Onset in adulthood Seizures Behavioral changes</td>
<td>Autoantibodies</td>
<td>NA</td>
</tr>
<tr>
<td>Perinatal brain injury</td>
<td>PKD, PNKD</td>
<td>Baseline neurological defects History of perinatal hypoxic encephalopathy or kernicterus</td>
<td>CSF abnormalities, low CD4 count, virus detection, positive TPHA/VDRL test Abnormal TSH, T4 levels</td>
<td>Normal or white-matter abnormalities</td>
</tr>
<tr>
<td>CNS infections (HIV, CMV, H1N1, syphilis)</td>
<td>PKD, PNKD</td>
<td>Onset in adulthood Baseline neurological defects</td>
<td>Autoantibodies</td>
<td>NA</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>PKD</td>
<td>Onset in adulthood Weight loss, muscle weakness, heat intolerance, anxiety</td>
<td>Abnormal TSH, T4 levels</td>
<td>NA</td>
</tr>
<tr>
<td>Medullary lesion</td>
<td>PKD</td>
<td>Baseline neurological defects</td>
<td>NA</td>
<td>Medullary lesion or malformation</td>
</tr>
<tr>
<td>Head or peripheral trauma</td>
<td>PKD, PNKD</td>
<td>Baseline neurological defects History of trauma</td>
<td>NA</td>
<td>Variable traumatic sequelae</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>PKD</td>
<td>Late onset Baseline neurological defects</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Methylphenidate treatment</td>
<td>PKD</td>
<td>Onset shortly after treatment initiation</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parasagittal meningioma</td>
<td>PKD, PNKD</td>
<td>Baseline neurological defects</td>
<td>Acanthocytes Hyperuricemia</td>
<td>Parasagittal meningioma NA</td>
</tr>
<tr>
<td>Neuroacanthosis</td>
<td>PKD, PNKD</td>
<td>Baseline neurological defects</td>
<td>Hyperuricemia</td>
<td>Normal or cerebral atrophy</td>
</tr>
<tr>
<td>Lesch-Nyhan disease</td>
<td>PKD, PNKD</td>
<td>Baseline neurological defects</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>PKD, PNKD</td>
<td>Psychological context Inconsistent manifestations &amp; clinical findings</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

MRI: magnetic resonance imaging; PKD: paroxysmal kinesigenic dysskinesia; PNKD: paroxysmal non-kinesigenic dysskinesia; PED: paroxysmal exercise-induced dysskinesia; EA: episodic ataxia; CSF: cerebrospinal fluid; NMO: neuromyelitis optica; CNS: central nervous system; NA: not available; PTH: parathyroid hormone; VGKC: voltage-gated potassium channel; HIV: human immunodeficiency virus; CMV: cytomegalovirus; TPHA: Treponema pallidum hemagglutination; VDRL: Venereal Disease Research Laboratory; TSH: thyroid-stimulating hormone.

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frequency ranging from once a month to several per day. Precipitating factors include sudden movement, startle response and stress. Intercritical examination reveals myokymias of the limbs and face. Affected individuals may also display delayed motor development, cognitive disability, epilepsy, choreoathetosis, neuromyotonia (muscle cramps and stiffness) and permanent cerebellar ataxia [75,116]. Acetazolamide and antiepileptic drugs can reduce the frequency and severity of attacks in some patients.

KCNA1 codes for the voltage-gated potassium channel Kv1.1, which is strongly expressed in the cerebellum, hippocampus and motor axons [74]. Most KCNA1 defects are missense mutations that impair channel dynamics, probably causing increased neuronal excitability [73]. There are no clear genotype-phenotype correlations [116].

2.8. The CACNA1A gene

Mutations in CACNA1A cause episodic ataxia type 2 (EA2) [117]. Inheritance is autosomal dominant with an estimated penetrance of 80–90% [118]. Onset is often in childhood or early adolescence. Attacks last longer than in EA1, from hours to days, but are less frequent, ranging from a few episodes per year to no more than several per week. Vertigo and nausea are frequently present. Triggering factors include stress, exercise and caffeine or alcohol intake [119]. While interictal examination may be normal early on, patients typically develop permanent interictal cerebellar ataxia and nystagmus. They may also have epilepsy, migraine, dystonia, fluctuating weakness and cognitive disability [73,120]. Acetazolamide is effective for paroxysmal episodes in two-thirds of patients [121,122]. The potassium channel blocker 4-aminopyridine can also help to control attacks [123].

CACNA1A encodes the pore-forming subunit of a voltage-dependent P/Q-type calcium channel that is strongly expressed in the cerebellum. Most mutations are likely to cause EA2 through loss of function, with subsequent impairment of synaptic transmission [119]. Interestingly, mutations in CACNA1A can cause other disorders through different pathogenic mechanisms [124], including familial hemiplegic migraine (FHM1) [117] and spinocerebellar ataxia type 6 (SCA6) [125]. There are clear genotype-phenotype correlations distinguishing these three disorders, albeit with some clinical overlap [126,127].

2.9. Secondary paroxysmal movement disorders

Numerous causes of secondary paroxysmal movement disorders have been reported in the literature (Table 2). These disorders are characterized by late onset, a negative family history, variable duration of attacks and triggering factors, and abnormal clinical or paraclinical findings [128]. The main causes are multiple sclerosis and other demyelinating disorders, often manifesting as brief and painful PxDs [128–145]. Treatment with antiepileptic drugs, especially carbamazepine, is usually beneficial. Other relatively frequent causes are vascular lesions and basal ganglia calcification [128,143,146–166]. A psychogenic origin of the PxD is frequent but often overlooked, accounting for 10% of PxD cases in a recent study [32,167–169]. Diagnostic clues include: (i) late onset; (ii) paroxysmal tremor; (iii) highly variable phenomenology, with variable duration and frequency of attacks and triggering factors; (iv) altered consciousness during attacks; and (v) atypical associated symptoms [169]. Multidisciplinary therapeutic approaches combining physiotherapy, cognitive behavioral therapy and/or hypnotherapy are helpful in some patients [92,169]. Other causes include encephalopathy, metabolic disorders (hypocalcemia, hypo- or hyperglycemia), central nervous system infections, head trauma and peripheral trauma, as well as other rare definite or possible causes (Table 2) [32,128,133,143,170–210]. Treatment is mainly focused on the underlying cause, especially when it is reversible. Antiepileptic drugs, benzodiazepines and botulinum toxin injections may also be beneficial.

3. Conclusion

New screening methods have enabled numerous culprit genes to be identified in patients with paroxysmal movement disorders, and more are likely to be discovered in the near future. These genetic advances have led to greater diagnostic certainty, improved genetic counseling, and targeted therapeutics. However, genetic diagnosis is sometimes hindered by a lack of reliable genotype-phenotype correlations, as a given phenotype may be caused by mutations in various genes. Multigene diagnostic panels should further improve the diagnosis of these rare but probably underdiagnosed disorders.

Disclosure of interest

The authors declare that they have no competing interest.

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