Chapter 9
Other Paroxysmal Movement Disorders

Roberto Erro, Kapil D. Sethi, and Kailash P. Bhatia

Introduction

Over the last years, a number of different genetic disorders have been reported to encompass recurrent episodes of dystonia, chorea, and/or myoclonus in their phenotype [1, 2]. Nonetheless, these disorders have escaped the classic definition of paroxysmal dyskinesia (PxD) and are not usually included in their classification (cfr. Chaps. 1, 3, 4, and 5). This probably owes to the fact that in these disorders the paroxysmal episodes of choreodystonia are usually embedded in complex neurological syndromes, which contrasts with the former diagnostic criterion for "*primary*" PxD requiring normal neurological examination between the attacks (cfr. Chap. 1). However, with the discovery of the genetic underpinnings of PxD, it has become clear that patients with the so-called "*primary*" PxD might in fact have interictal findings on examination or other associated features by history (PxD associated with *SCL2A1* mutations, for instance, cfr. Chap. 5). Therefore, additional (interictal) findings on examination should be no longer considered an exclusionary criterion for PxD [1] but should be instead carefully investigated as these might be helpful in guiding subsequent diagnostic workup.

R. Erro (✉)
Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana",
University of Salerno, Baronissi, SA, Italy
e-mail: rerro@unisa.it

K. D. Sethi
Georgia Regents University, Augusta, GA, USA

K. P. Bhatia
Department of Clinical and Movement Neurosciences, UCL,
Queen Square Institute of Neurology, London, UK

This also implies that the differential diagnosis in patients presenting with episodic choreodystonia should not only include the disorders associated with the three main form of PxD [i.e., kinesigenic (PKD), non-kinesigenic (PNKD), and exercise-induced (PED)] but also a number of different conditions, which can encompass paroxysmal choreodystonia in their phenotype. Differently from the main three forms of PxD, which are primarily characterized based on the specific triggers of the episodes, the ones covered in this chapter can also be defined by other features including the distribution of choreodystonia during the attacks.

ADCY5 Mutations

Mutations in *ADCY5*, encoding for the adenylate cyclase 5, can cause a spectrum of non-paroxysmal, childhood-onset, movement disorders that might include chorea, dystonia, and myoclonus, or a combination thereof, sometimes associated with axial hypotonia and also PxD [3, 4]. PxD does not always fit clearly within previously identified PxD subtypes. The myoclonus may involve the face, and the attacks can be painful [similar to alternating hemiplegia of childhood (AHC); see below], a point of difference from PxD due to *PRRT2*, *PNKD*, or *GLUT-1* mutations (i.e., the main causes of PKD, PNKD, and PED, respectively) [5, 6] Moreover, *ADCY5*-PxD may manifest within the same patient as multiple subtypes, including both PKD and PNKD [5, 6]. Two unrelated *ADCY5* carriers manifesting with attacks similar to those observed in AHC have been recently reported in the context of a more complex neurological picture including dysarthria, hypotonia, and *non*-paroxysmal choreodystonia [7], reinforcing the concept that episodic movement disorders due to *ADCY5* mutations can be quite variable.

Further at variance with other genetic disorders that can produce PxD, patients with *ADCY5* mutations characteristically develop PxD during sleep [6]. Nighttime dyskinesia (along with the presence of non-paroxysmal movement disorders) would therefore suggest *ADCY5* mutations. However, nighttime PxD (formerly referred as to paroxysmal hypnagogic dyskinesias, a fourth subtype of PxD; cfr. Chaps. 1 and 2) has been also rarely reported in association with *PRRT2* mutations [8], which should be therefore considered in such cases.

Treatment can be disappointing, but a partial benefit has been reported with both tetrabenazine [9] and deep brain stimulation [10].

ATP1A3 Spectrum Disorders

Mutations in the *ATP1A3* gene can cause a number of different clinical syndromes including AHC, rapid-onset dystonia parkinsonism, and cerebellar ataxia with pes cavus and optic neuropathy, although an increasing number of patients with

overlapping phenotypes have been recently described [11, 12]. In the context of this chapter, we will only cover AHC, which is classically a sporadic disorder with onset within the first 18 months, by definition [11, 12]. The misnomer AHC is explained by the first descriptions of this condition that focused on the occurrence of episodic hemiplegia. In fact, attacks of hemidystonia occur at least as commonly as the attacks of hemiplegia, may involve both sides of the body at the same time, and may encompass other paroxysmal neurological signs including nystagmus, anarthria, dysphagia, and seizures [11–13]. Paroxysmal eye movements are very characteristic. Attacks last from a few minutes, rarely, to several days, and episodes occur from repeatedly within a day to several times a month [11–13]. They are almost invariably triggered by emotional stressors, such as excitement, or less frequently by physical stressors, including hypo- or hyperthermia, respiratory tract infections and surgery [11–13]. Characteristically, there is a rostrocaudal gradient in the hemiplegic/hemidystonic episodes (face/neck>arm>leg). Episodes, either hemiplegic or hemidystonic, typically shift from one side of the body to the other and are typically ameliorated by sleep. Almost invariably the attacks are associated with other (interictal) features such as developmental deficits, muscular hypotonia, dysarthria, and ataxia [11–13]. However, "milder" forms with age at onset >18 months, with focal presentation of dystonic attacks (predominantly affecting the arm), and with no other associated signs either during the episodes or interictally (Video 9.1) have been recently reported [14]. Long duration of the episodes (up to days), painful dystonic posturing, and sleep-induced cessation of the attacks are clinical clues to suspect *ATP1A3* mutations.

Treatment consists of flunarizine (10–20 mg/day) as a prophylactic drug along with the avoidance of triggers [11–13]. Patients should be encouraged to sleep when attacks begin, using fast-acting benzodiazepines if necessary.

SCN8A Mutations

Mutations in *SCN8A*, encoding for sodium voltage-gated channel alpha subunit 8, have been recently reported to be an alternative cause of the ICCA syndrome (i.e., infantile convulsions with choreoathetosis, which is mostly associated with *PRRT2* mutations, cfr. Chap. 3) [15]. However, this proposal has been questioned [16] based on the evidence that, in one affected case, a "PKD" attack was recorded by video-electroencephalography and correlated to a cortical event, suggesting that these attacks might in fact be epileptic in nature. Moreover, in this single report where the term PKD was used, attacks were not induced by sudden movements [15]. We therefore feel that the term PKD in the context of *SCN8A* mutations is a misnomer. However, it has to be acknowledged that *SCN8A* mutations have been in other reports associated with episodic dystonia (with no kinesigenic triggers), although the term paroxysmal dyskinesia was not explicitly used [17]. As such, it is worth considering this condition in the differential diagnosis of childhood-onset

PxD, especially of the non-kinesigenic variant and, when associated with epileptic seizures, particularly those resistant to antiepileptic therapy and/or with neurodevelopmental delay [17].

CACNA1A Mutations

Mutations in the *CACNA1A* gene, which encodes for the calcium voltage-gated channel subunit alpha1 A, are associated with a number of phenotypes including SCA6, episodic ataxia type 2 (see Chap. 11), as well as familial hemiplegic migraine. More rarely, *CACNA1A* mutations have been associated with episodes of benign paroxysmal torticollis of the infancy (BPTI) [18, 19]. BPTI is characterized by attacks of head tilt with onset within the first 18 months of life with a tendency to remission with increasing aging [18, 19]. Episode duration ranges from 10 min to several days, and associated features can be vomiting, pallor, and ataxia [18, 19]. As mentioned above, BPTI usually resolves after infancy but can be sometimes replaced by paroxysmal vertigo and/or migraine [18, 19]. The co-occurrence of episodic ataxia, hemiplegic migraine, and paroxysmal tonic upgaze in a single subject or in the family are a clue to suspect *CACNA1A* mutations, even though in many BPTI cases the genetic cause is not found [20]. This condition is generally self-limiting, and usually no treatment is needed.

SLC16A2 Mutations

The monocarboxylate transporter type 8 (MCT8), encoded by *SLC16A2,* is required for transmembrane uptake of free triiodothyronine (fT3) from blood into neurons. MCT8 deficiency causes an X-linked disorder (also termed Allan-Herndon-Dudley syndrome), with onset in infancy and characterized by hypotonia with poor head control, generalized muscular hypotrophy, microcephaly, and marked developmental delay [21]. The disorder is progressive, and a different combination of spasticity, ataxia, and severe dysarthria usually develops and complicates the clinical syndrome. In a subset of cases, a specific sort of PKD is observed [21, 22]. Attacks are classically triggered by sudden passive movements such as changing of clothes or diapers or by lifting the children from one place to another [21, 22]. Attacks can further be triggered by excitement, happiness, or crying, thus falling into the PNKD subtype. Episodes are generally brief, lasting seconds to few minutes, and the main phenomenology is dystonia. The hallmark of MCT8 deficiency is raised serum concentration of fT3 [21]. At present, no treatment is available, and management is symptomatic and supportive.

References

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