Movement Disorders
CLINICAL PRACTICE
REVIEW

Scoping Review on ADCY5-Related Movement Disorders

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ABSTRACT: Background: Adenylyl cyclase 5 (ADCY5)-related movement disorder (ADCY5-RMD) is a rare, childhood-onset disease resulting from pathogenic variants in the *ADCY5* gene. The clinical features, diagnostic options, natural history, and treatments for this disease are poorly characterized and have never been established through a structured approach.

Objective: This scoping review attempts to summarize all available clinical literature on ADCY5-RMD.

Methods: Eighty-seven articles were selected for inclusion in this scoping review. The majority of articles identified were case reports or case series.

Results: These articles demonstrate that patients with ADCY5-RMD suffer from permanent and/ or paroxysmal hyperkinetic movements. The paroxysmal episodes can be worsened by environmental triggers, in particular the sleep–wake transition phase in the early morning. Occurrence of nocturnal paroxysmal dyskinesias and perioral twitches are highly suggestive of the diagnosis when present. In the majority of patients intellectual capacity is preserved. ADCY5-RMD is considered a non-progressive disorder, with inter-individual variations in evolution with aging. Somatic mosaicism, mode of inheritance and the location of the mutation within the protein can influence phenotype.

Conclusions: The current evidence for therapeutic options for ADCY5-RMD is limited: caffeine, benzodiazepines and deep brain stimulation have been consistently reported to be useful in case reports and case series.

Adenylyl cyclase 5 (ADCY5)-related movement disorder (ADCY5-RMD) is a rare, childhood-onset disease resulting from pathogenic variants in the *ADCY5* gene. The disease is mainly characterized by the presence of hyperkinetic movements. The condition was first described in 2001 and called "familial dyskinesia and facial myokymia" at that time.[1] The phenotype was linked to the chromosomal region 3p21-3q21 in 2009, and then with variants in *ADCY5* in 2012.[2,3] The disease may be caused by monallelic variants (autosomal dominant) or more rarely biallelic variants (autosomal recessive).[3–9]

The levels of cyclic AMP (cAMP) in the striatum is involved in the fine regulation of movement execution, modulating facilitatory and inhibitory outputs.[10] Alteration of the striatal cAMP turnover is involved in many hyperkinetic movement disorders such as levodopa-induced dyskinesia, chorea in Huntington's disease, and hyperkinetic movements associated with mutations in *GNAO1*, *GNAL*, *GNB1, PDE10A* or *PDE2A*.[10] Adenylyl cyclase five catalyzes the production of striatal cAMP from ATP, and the molecular pathogenesis of ADCY5-RMD mostly involves perturbations in the striatal cAMP synthesis pathway.[10] Most monoallelic pathogenic missense *ADCY5* variants likely act through a gain-of-function mechanism and increase cAMP levels in striatal projection neurons, whereas several other variants, including biallelic pathogenic variants, likely cause loss-of-function.[5,7,8,11–13]

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The natural history of ADCY5-RMD is poorly understood and the best diagnostic clues have not yet been established through a structured approach. Consequently, patients often have a long diagnostic delay and are often misdiagnosed. Medications reported to be beneficial in certain patients have also been reported to worsen symptoms in others. There is no consensus or guideline on therapeutic options for these patients, nor are there systematic or scoping reviews on ADCY5-RMD. Through this scoping review, using a comprehensive, structured approach, we aim to characterize the clinical features, diagnostic options, natural history, and treatment options for ADCY5-RMD.

Methods

Protocol and Registration

This scoping review included the 6-step framework recommended by Arksey and O'Malley, with enhancements from Levac et al, and Joanna Briggs Institute.[14–16] The review protocol is available online at https://osf.io/jrd8p/. The scoping review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta Analyses extension for scoping reviews.[17]

Identifying the Review Question

This scoping review attempts to summarize all available clinical literature on ADCY5-RMD, to identify key concepts and knowledge gaps. The main purpose was to identify diagnostic clues for ADCY5-RMD and treatments options, but also to clarify the natural history of ADCY5-RMD, including the effect of specific mutations and long-term effect of the treatments.

Identifying Relevant Studies

The electronic databases of Medline (Ovid), Embase, Cochrane Central Register of Controlled Trials and CINAHL plus were searched. The search terms included known medical subject headings, such as adenylyl cyclase, dyskinesias, dystonia. The exact search terms are included in Supplementary Table S1. The searches were conducted and took into account articles published on and up to the September 21, 2022.

Eligibility Criteria. Any study describing human patients, from any geographic location, including individuals of any ethnicity, gender and age with ADCY5-RMD were included. All types of studies including randomized controlled trials, non-randomized controlled trials, before and after studies, interrupted time-series studies, analytical observational studies including prospective and retrospective cohort studies, case–control studies, analytical cross-sectional studies, case series, individual case reports, descriptive cross-sectional studies, systematic reviews, text and opinion papers and congress poster or oral presentations were considered for inclusion in this scoping review. Animal based studies and articles not in English, Spanish, French or German, were excluded.

Study Selection

The combined database search was collated, imported into Covidence and duplicates were removed. Studies focusing on clinical features, genetic information, diagnostic tests, treatment, and management options for ADCY5-RMD were selected. Four reviewers (PM, CN, TP, ER) independently screened titles and abstracts for assessment against the inclusion criteria for the review. Any disagreements that arose between the reviewers were resolved by the reviewers TP or ER. For the selected titles and abstracts, full text articles were obtained and reviewed in duplicate for fulfillment of the inclusion criteria.

Charting the Data

Data extraction was divided among two authors (PM, CN), with verification of the extracted information by two other authors (TP, ER). The data extraction form used to tabulate pertinent information is included as Supplementary Table S2.

Collating, Summarizing and Reporting the Results

Analysis of the selected studies was presented through descriptive methods (quantitative and qualitative) of the information relating to diagnosis and treatment of ADCY5, using the data extraction form. Study characteristics, population characteristics, and the diagnostic or treatment issues studied was also documented. Variants were described according to the Human Genome Variation Society nomenclature and the reference variant used in the article is NM_183357.3. Supplementary Table S3 summarizes the included studies.

Results

Selected Studies

Out of 582 studies screened initially, 485 were excluded at the stage of abstract screening. These studies predominantly described experiments on animal or cellular models, or they related to the role of ADCY5 in Diabetes. Ninety-three full text articles were then reviewed for eligibility, out of which 75 studies were included. The search was re-executed on September 21, 2022, with an additional 163 abstracts screened. Twenty-one full text articles were reviewed for eligibility, and 12 studies were included. In total, 87 (75+ 12) articles were included in this review (Fig. 1).

Article Characteristics

The majority of the included articles were published in or after 2015 (82/87). The majority of the articles were published by centers in the United States (19/87), followed by Germany (12/87) and the United Kingdom (12/87) respectively. 74/87 of articles were from high income countries according to the 2021–2022

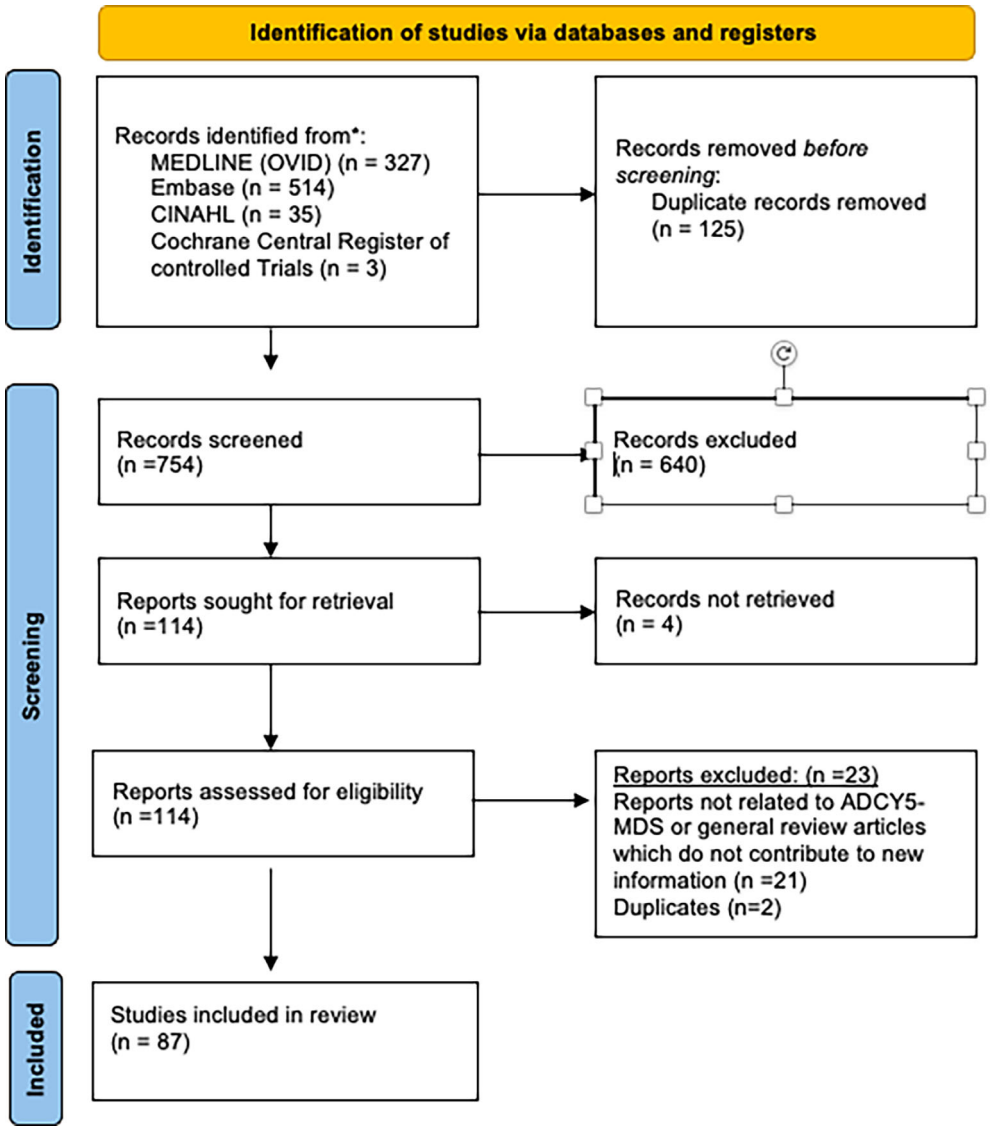

Figure 1. Study selection flow diagram.

World Bank Classification and no article was from a low-income country.[18] The majority of articles were case reports or case series (52/87).

ADCY5-RMD

Clinical Features and Phenomenology

ADCY5-RMD is characterized by a variable combination of hyperkinetic movements, most commonly focal or generalized chorea, dystonia and myoclonus.[19–25] (Supplementary Table S4) There is a predilection of the myoclonus and chorea for facial muscles (perioral and periorbital).[1,2,26]

Chorea or choreoathetosis can be focal or generalized, and typically increases with voluntary action.[19,21,27] Dyskinesias are sometimes described as ballistic movements.[11,19,28,29] Dystonia is also variable in ADCY5-RMD and may affect the trunk,[30,31] neck,[32–34] limbs[7,32,35,36] and/or extremities[21] (including writer's cramp).[37] Less frequently patients present with orolingual dystonia,[30] blepharospasm[34] or Meige's syndrome.[38,39] Likewise, patients can have action or rest tremor[30] which can affect the head,[1,11,30] the limbs[7,27] and the hands.[30,40] Bilateral bradykinesia was reported in one 13-year-old boy.[41]

Many patients also have axial hypotonia,[11,19] often associated with a more severe phenotype, necessitating use of a

frog-like method of ambulation.[19,21,22,27] In a cohort study including 30 patients with ADCY5-RMD, 50% (15/30) had hypotonia and 60% (18/30) had gait disorders.[42] Patients can present with axial weakness,[27] limb weakness[37,41] and muscular atrophy.[13] One 15-year-old girl was reported to have generalized weakness, poor head support due to marked neck muscle weakness and camptocormia.[11] A few patients have been described with limb spasticity (increased tone, hyperreflexia, extensor plantar reflexes).[7,19,27,31,43] The ADCY5 phenotype has been extended to spastic paraparesis in a minority of patients.[37,40]

Gait impairment and falls can be due to the hyperkinetic movements, spasticity and/or axial hypotonia.[5,19,21–23,30,31,35,38,44–48] There is usually no cerebellar or proprioceptive ataxia.[1,13] Mild dysmetria and dysdiadochokinesia[1,41,49] associated with uncoordinated or unstable gait have been anecdotally reported.

Dyskinesia can affect the tongue,[11,32,34] resulting in speech impairment. Mild to severe dysarthria is present in the majority of patients[5,11,23,29,30,32,34,35,41,44,47,49,50] (in 63% [19/30] of patients in the largest series).[42]

Symptom severity is also quite variable, with some patients having subtle choreic/myoclonic upper limb movements, which may resemble myoclonus-dystonia or benign hereditary chorea.

Paroxysmal Episodes

ADCY5-RMD commonly presents with paroxysmal worsening of the hyperkinetic movements superimposed on the permanent movement disorder.[11,27,32] In Méneret et al's study, 90% (27/30) had baseline hyperkinetic movement disorders (dystonia, chorea, myoclonus, tremor, or various combinations) and 93% (28/30) had paroxysmal movement disorders (73% with nocturnal events).[42]

Phenomenology of the Paroxysmal Episodes

Attacks typically consist of chorea or dystonia affecting the face, limbs, neck or/and trunk. These attacks can occur during daytime or nighttime. The associated movements, degree of posturing and patterned features (eg, jerky or tremulous) are variable between individuals.[5] The dystonic attacks may comprise spasms with back arching, toe curling, and upper limb extension.[19,22,44,45] Other paroxysmal episodes are characterized by sudden hip and trunk flexion causing patients to fall.[21] Speech (but not language) can be altered during paroxysmal episodes due to hyperkinetic movements of the orofacial and/or laryngeal area. Attacks of painful orobuccal movements can result in intermittent states of almost complete dysarthric mutism.[22]

Some patients have paroxysmal events which resemble alternating hemiplegia of childhood.[49,51–53] These events start with facial weakness and progress to limb involvement in a variable distribution but commonly in a hemiplegic fashion.[49]

Paroxysmal events can be painful, limit mobility[19] or lead to falls and self-injury.[33] Some patients have limited responsiveness during these episodes despite remaining alert.[21,22,37,54]

Characteristics of the Attacks: Duration, Frequency and Triggers

Frequency and duration of paroxysmal dyskinetic episodes are variable. They may occur up to 40 times a day[42] and last seconds,[21,46,49] minutes[24,28,33,35,44,55,56] or hours.[19,30,35] Beyond the well-characterized paroxysmal events, some patients with ADCY5-RMD describe fluctuations in severity of the movement disorder with no clear onset or offset. Fluctuations can occur within periods in a day,[47] last for a few days or weeks,[11,35] or even a few months. These periods of worsening may be followed by long quiescent periods.[11,35] These fluctuations typically lack precise triggers.[19]

For the paroxysmal exacerbation of movement disorders, several triggers have been reported, of which the most common are emotions/anxiety/stress.[1,19,21,27,30,32,46,57,58] Tiredness[21,30,51] and action[19,27,32,58] are also reported. Anecdotally, mental activity,[19,30] temperature changes/heat,[19,32,35] laughter, sneezing[19] and hunger have been reported as triggers.[35] Paroxysmal movements were exacerbated by menstruation in two women.[27,58] Medications, including antihistamines such as diphenhydramine and beta 2 adrenergic receptor agonists exacerbated the paroxysmal movements in one case.[54] Alcohol does not seem to be a trigger[1,30] and even partially improved motor symptoms in one woman.[54]

Intercurrent illnesses were reported to provoke dyskinetic episodes in several patients with ADCY5-RMD.[19,27,58–61] There is one case report of persistent unrelenting "dyskinetic storms" triggered by an acute respiratory tract infection.[33]

The Particular Case of Paroxysmal Nocturnal Episodes

Among the paroxysmal hyperkinetic episodes, occurrence of paroxysmal episodes upon sleeping lasting up to 30 minutes and starting as early as the age of one is a characteristic feature of ADCY5-RMD.[11,27]

Chang et al described seven patients with ADCY5-RMD who all reported exacerbations of dyskinesia that interrupted sleep, without EEG evidence of seizure activity.[19] On polysomnography, choreoathetosis was exacerbated during both drowsiness and during sleep arousal.[19] The specific timeline of nocturnal dyskinesias during sleep was assessed in a case–control study which compared video polysomnography results in seven patients with ADCY5-RMD and 14 controls.[50] It showed that nocturnal paroxysmal dyskinesias are not due to a primary sleep disorder but were elicited by a wake-related trigger and therefore prevent patients from returning to sleep immediately.[50] Dyskinesia occurred more frequently during morning awakenings compared to awake periods before falling asleep.[50] The frequent and prolonged awakenings secondary to

the abnormal movements result in lower sleep efficiencies in patients, in accordance with prior findings in three adult males with ADCY5-RMD.[56]

Other Neurological Manifestations

Oculomotor Signs

Abnormal smooth pursuit movements have been described in several reports.[7,23,30] A detailed eye movement examination in three adult males with ADCY5-RMD found oculomotor apraxia with gaze limitation more pronounced in the vertical plane.[56] There were difficulties initiating and executing full-range saccades, especially in the vertical plane, which improved with head thrusts or with reinforced sensory stimulation. Saccadic velocities were preserved in all patients. In six non-related patients reported by Chang et al, five had abnormal saccades: four had absent saccadic upgaze and one had prolonged vertical saccadic latencies.[19] All subjects had normal pursuits. Another report described hypometric saccades and prolonged vertical and horizontal latencies in one patient.[41] Ocular convergence spasms have been described in one girl with bi-allelic mutations of the ADCY5 gene.[8] Intermittent upward tonic eye deviations have also been reported in a 2-year-old boy.[7]

Intellect

The majority of patients have normal intellectual capacity.[13,35] In Méneret et als study, 43% (13/30) had attention deficits.[42] Intellectual disability (often mild) was reported in 5 of 20 cases in Chen et als study,[35] and several case reports/studies.[7,9,19,21,27,31,44,47,54,62] Severe intellectual disability was described in individuals with bi-allelic mutations (recessive form), associated with developmental delay and severe neurological manifestations.[7–9]

Developmental Delay

In the majority of patients, motor and speech developmental milestones are delayed[5,7,9,11,21,23,24,27,29,31–35,37,38,45–47,49,60,62–67] sometimes severely[41] (especially in homozygous mutations[8]). Five of the seven patients described by Chang et al were speaking single words between age 2 and 7; three acquired normal language ability later.[19] Mobility largely depends on associated axial hypotonia and action-induced episodic dyskinesia.[19]

Tics

Rarely, ADCY5-RMD can involve tics: A 12-year-old girl presented with tics and obsessive-compulsive symptoms and coprolalia[37]; a 11-year-old boy had antisocial behavior associated with tics.[62]

Psychiatric Symptoms

Vijiaratnam et al described a male with ADCY5-RMD who presented from his midteens with depressive symptoms and anxiety.[54] He was hospitalized twice in his 20s, once with acute psychosis and another time following a suicide attempt. His mother, who was also affected by ADCY5-RMD, had depression and anxiety and died by suicide at the age of 26. Chen et al reported psychosis in two patients.[35]

Obsessive-compulsive behavior with anxiety, phobias, and grinding movements were reported in three young siblings.[7] Obsessive-compulsive symptoms, along with anxiety disorder with phobias was also reported in a 12 year old girl.[37] Kaiyrzhanov et al suggested that psychosis and depression tend to develop in adults, while younger patients present typically with obsessive-compulsive behavior and anxiety.[7]

Disruptive social behavior (stealing, lying, aggression against others, vandalism), in addition to depression, was also described in an 11-year-old boy with ADCY5-RMD.[62] Difficulties in peer relationships was described in a 14-year-old girl, associated with attacks of rage, and depression.[23]

Other Systemic Manifestations

Dilated cardiomyopathy and hypothyroidism have been reported in a few patients with ADCY5-RMD.[3–5,7,64] One 46-year-old man was diagnosed with severe dilated cardiomyopathy. Four of his neurologically affected relatives also had congestive heart failure, as early as in their fifties for one, and causing death in at least three of them.[3] Young-onset cardiomyopathy was also described in two young females with homozygous variants in ADCY5.[5,7] This suggests patients with ADCY5-RMD should ideally have an echocardiogram and thyroid function testing, at least until it has been definitely established whether cardiac and thyroid involvement are part of the phenotype.

Diagnosis

Patients with ADCY5-RMD are often misdiagnosed as dyskinetic cerebral palsy or sleep related hypermotor epilepsy, highlighting the importance of carefully phenotyping patients and better informing physicians on the clinical spectrum. As the diagnosis influences the therapeutic strategy, it is important to make an early diagnosis.

Genetic testing, consisting of sequencing of the *ADCY5* gene should be done in patients with a phenotype consistent with this diagnosis.[8,32] Given how rare this disorder is and its phenotypic variability, cases are often incidentally diagnosed with whole exome or whole genome sequencing studies.[11,13,28,29,34] The presence of mosaicism is of prognostic significance and should be considered, especially when the phenotype is mild. Importantly, to detect mosaic cells, you often need to increase the read depth and/or perform allele-specific PCR.[68]

Diagnostic tests such as brain MRI and biochemical markers are typically normal.[32,46,69] On brain MRI one patient had delayed myelination, and another patient had a leukoencephalopathy and

mild cerebellar vermian atrophy.[8,40] It is not clear whether these very rare findings are related to the ADCY5 disorder.

Natural History

ADCY5-RMD is a childhood-onset disorder, with symptom onset ranging from 6 months to 10 years of age.[4,29] The hyperkinetic movements begin most frequently between 1 to 4 years of age.[27,30,35,43,45,62,63] There are isolated case reports of symptom onset as young as 2 months of age.[35] Infants who are unwell due to other systemic processes (eg, febrile illness or pre-term delivery) can have an earlier age at onset, along with developmental regression.[21,27] Developmental issues and motor problems might start in the pre-natal period, with decreased intrauterine movements.[5]

The infantile period can be characterized by hypotonia, poor suck and failure to thrive.[9,45] An exaggerated Moro reflex has also been noted.[27,35] There can be a delay in motor development, with reports of unsupported sitting occurring at 15–18 months and walking with the assistance of a walker at 30 months–3 years.[11,27] There are also reports of delayed speech development possibly related to facial dyskinesia.[19,38]

ADCY5-RMD is considered a non-progressive disorder, with inter-individual variations in evolution with aging. Some reports describe an improvement in frequency and severity of the paroxysmal episodes in the 30s, while others describe a worsening in frequency with age, with episodes becoming nearly constant by the age of 30.[2,19] In general, the chorea and ballistic episodes are thought to improve during the teenage years, with the phenotype changing to dystonia and myoclonus.[20] The disorder can also become milder and non-progressive in adulthood, but complete remission is rare; with one case report describing a patient who had a nearly normal neurological examination by the age of 68.[31,35] However, worsening of episodic dyskinesia led to motor regression and loss of ambulation in early adulthood in two cases.[19]

Symptoms have been described to reduce during pregnancy.[54] Spasticity is a later onset phenomenon, with symptoms reported in the 30s in one individual, and worsening with time in another report.[37,40] Despite significant disability, the lifespan is not thought to be affected by the disorder, although relevant data are lacking.[2] This could be a subject of future study as functional variants of *ADCY5* or modulation of AC5 activity, have been linked to longevity in various models.[70,71]

Genotype–Phenotype Correlation

The structure of AC5 protein is shown in Figure 2A.

Most mutations in *ADCY5* are missense variants. Frameshifts, splice site variants and indels have also been occasionally reported[27,34] but no large deletions or duplications have been reported. The phenotype is affected by the location of the mutations within the protein. The C1b domain mutation c.2176G > A p.(Ala726Thr) may be associated with the mildest disease.[35] Axial hypotonia is a common finding in patients with all mutations, except those in C1b.[35] Mutations in the C1a and C2a domain cause moderate to severe disorders.[35] Mutations in the C1a domain affecting the amino acid residue Arginine 418 are recurrent, suggesting that this residue is important for the function of the protein.[35] Patients with mutations involving this residue seem to have a more severe presentation, with 78% having onset in infancy, 71% nocturnal movements, 79% paroxysmal worsening, 86% axial hypotonia, 43% painful dystonia, 71% facial movements, and 36% brisk reflexes.[35] Mutations in the M1 and M2 domain have been associated with a spastic paraparesis phenotype.[37,40]

While most mutations described in ADCY5 are inherited in an autosomal dominant manner, sporadic/ de novo pathogenic variants are not rare.[13,19,21,27,28,31,34,35,37,46,65,72,73] Autosomal recessive inheritance of ADCY5-RMD has been described in five families.[5–9] The variants noted in families with recessive inheritance include: homozygosity for the missense mutation c.1762G > A p.(Asp588Asn), homozygosity for the missense variant c.1406G > A p.(Ser469Asn), homozygosity for the splice donor variant c.897 + 1G > T, homozygosity for the missense variant c.3712C > T p.(Arg1238Trp), compound heterozygosity for the frameshift variant c.409_428del20 p.(Gly137Cysfs*184) and the missense variant c.3037C > T p.(Arg1013Cys).[5–9] These bi-allelic mutations tend to affect the C1 domain.[5,7,9] The autosomal recessive nature of these variants as well as in silico models, suggests a loss of function mechanism, contrasting with the previously considered gain of function mechanism for missense variants in *ADCY5*.[5,7,8] The affected individuals in four out of these five families with recessive inheritance had a severe phenotype including psychiatric manifestations, intellectual disability and developmental delay.[5,7–9]

Genetic mosaicism is the presence of two or more cell lineages with different genotypes in a single individual.[74] Genetic mosaicism has been noted in patients with ADCY5-RMD and seems to be relatively frequent among ADCY5 patients. These patients typically display milder phenotypes, mostly just exhibiting pure paroxysmal episodes with preserved ambulation and no other clinical features.[55,75] Somatic mosaicism could also partly account for intra-familial clinical variability in cases of ADCY5-RMD who carry the same mutation.[35]

Medications

There are currently no randomized controlled trials or consensus guidelines on therapeutic options for ADCY5-RMD. Case reports indicate that benzodiazepines such as clonazepam (0.5–2 mg/ daily), clobazam (0.2 mg/kg), diazepam and lorazepam can be useful to treat dyskinetic episodes especially those associated with sleep.[5,19,21,23,27,46,51,55] Clonazepam has also been reported to reduce axial hypotonia and truncal extension dystonic spasms in some patients.[19] Propranolol has been beneficial in case reports for chorea.[30,43,76] Acetazolamide has been successful in a few case series, but it has also been ineffective or worsened episodes in eight patients.[2,21,42,77] Chlordiazepoxide, trihexyphenidyl (3–7.5 mg/d) and tetrabenazine (50–75 mg/d), decreased the

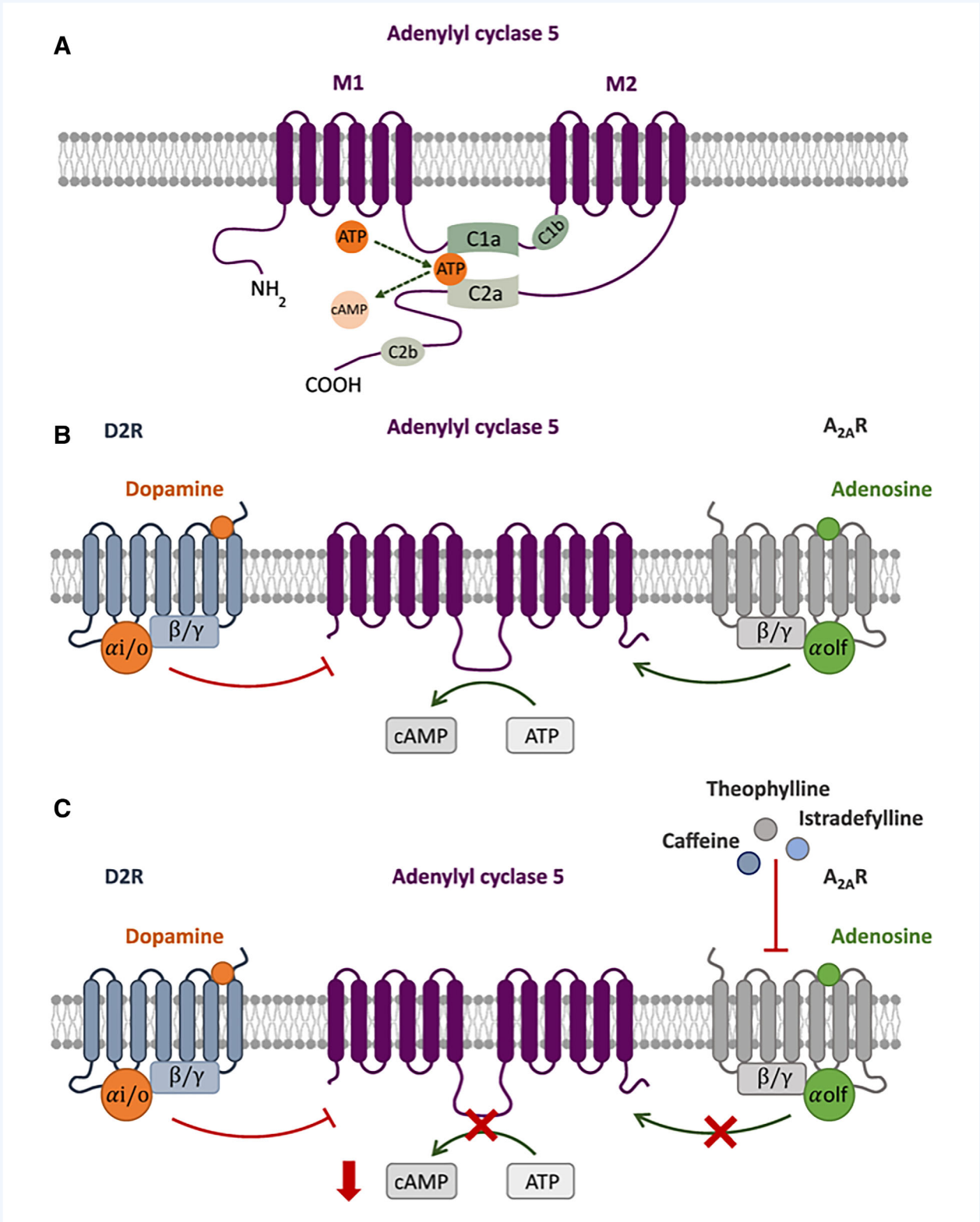

Figure 2. (A) Schematic representation of AC5: demonstrating the 2 membrane-spanning domains (M1 and M2) containing 6 helixes each, and 2 cytoplasmic domains (C1 and C2), divided into a and b. The catalytic domain C1a and C2a form an ATP-binding pocket converting ATP into cAMP. (B) Modulation of cyclic AMP synthesis pathway in striato-pallidal neurons of the indirect pathway: cAMP catalyzation by AC5 is regulated by G protein-coupled receptors adenosine A_{2A} receptors ($A_{2A}R$) and dopamine D2 receptors (D2R). The positive regulation occurs through Gαolf after activation of the $A_{2A}R$, and the negative regulation occur through Gαi/o after activation of the D2R. (C) $A_{2A}R$ antagonists, such as caffeine, istradefylline or theophylline reduce the activity of Gαolf and, in turn, cAMP production.

frequency and intensity of paroxysmal events in a few case reports.[5,33,35,59,65] However, in three cases, tetrabenazine worsened the movement disorder or provoked calf dystonia.[27,42]

In striatal neurons, the dopaminergic and adenosinergic neurotransmission regulate the level of cAMP through the activation of G protein coupled receptors.[10,44,51] (Fig. 2B) Most pathogenic variants causing ADCY5-RMD are believed to be gain of function mutations resulting in increased cAMP levels in striatal neurons. The therapeutic effect of adenosine 2A (A2A) antagonists on hyperkinetic movement disorders is thought to mostly occur through reduction of cAMP levels in the striato-pallidal projection neurons (Fig. 2C).

The pure A_{2A} receptor antagonist istradefylline has been shown to improve chorea-dystonic movements, dexterity and gait in one patient with ADCY5-RMD.[44] Caffeine is another A_{2A} receptor antagonist that has been shown to dramatically decrease paroxysmal dyskinesias in patients with ADCY5-RMD.[55,72] In the only study of a large series of patients focusing on therapeutic aspects, 30 patients who had tried caffeine for ADCY5-RMD were surveyed.[42]

87% of these patients reported at least a 40% improvement in the hyperkinetic involuntary movements with caffeine.[42] Improvement was also noted in other features such as gait, hypotonia, dysarthria, pain, attention and concentration, sleep quality, mood, fine motor skills, and drooling in this cohort.[42] This latter paper also highlighted the other medications used in this cohort and the frequent futile therapeutic trials, with a total of 114 therapeutic trials with 30 different drugs performed in these 30 patients.[42] The treatments that were most often considered to be effective in this cohort were: deep brain stimulation (DBS) of the globus pallidus internus (GPi) (3 of 4), clonazepam (5 of 15), diazepam (4 of 6), tetrabenazine (3 of 9), baclofen (2 of 4), levetiracetam (2 of 5), and trihexyphenidyl (3 of 13).[42] Caffeine has been rarely reported to worsen individual cases.[27]

Another A_{2A} receptor antagonist, theophylline, has shown to reduce ADCY5-catalyzed cAMP production in ADCY5 R418W mutant non-neuronal cells.[61] In one preschool aged patient with ADCY5-RMD, a slow-release formulation of theophylline significantly improved his hypotonia, paroxysmal dyskinesia, nocturnal episodes/quality of sleep, and ambulation.[61]

There are isolated reports demonstrating the benefit of other medications, for example, methylphenidate improved chorea, paroxysmal episodes of weakness, dysarthria, attention, concentration and motor skills in one patient. Levodopa improved axial hypotonia, dystonic spasms, hypophonia and speech.[19,45] However, in one case report levodopa was thought to result in hypotonia and in 15 other patients it was ineffective or worsened their episodes.[42,54,67] Carbamazepine and oxcarbazepine improved dyskinesia in case reports.[19,78] The combination of baclofen, trihexyphenidyl and prednisolone slightly improved symptoms in one case.[54] The symptoms were partially alcohol-responsive in one case report.[54]

Deep Brain Stimulation

Bilateral pallidal DBS can markedly reduce the permanent hyperkinetic movement disorders and paroxysmal episodes in ADCY5-RMD.[10,19,32,45] It has been used in emergency situations in patients who have a dyskinetic storm.[33] It can also improve tongue and facial dyskinesia as well as speech.[45,79] It has also been shown to improve nocturnal exacerbations.[32] Axial dystonia may be less responsive.[19] There is generally a partial improvement post DBS, but patients still remain significantly impaired and it does not always translate to an improvement in activities of daily living.[32] ADCY5-RMD patients obtain less benefit from DBS in comparison with DYT-*TOR1A*.[80] The symptoms may be most responsive immediately post stimulation with movements re-emerging gradually in the weeks after.[32] However, on stopping stimulation, the symptoms have been shown to worsen irrespective of the duration post stimulation.[27]

Discussion

Main Findings

This scoping review summarizes the existing literature on ADCY5-RMD and provides insight into the clinical features, natural history, diagnostic journey and therapeutic strategies. The core phenotype comprises a hyperkinetic movement disorder (dystonia, chorea, myoclonus and/or tremor) that can be paroxysmal, permanent or, typically, a combination thereof. In most patients, the hyperkinetic movements are mixed. Other features include axial hypotonia, speech disturbance, oculomotor signs and pyramidal dysfunction. Intellectual disability (usually mild) and psychiatric disorders have been occasionally reported.[11,19,21,22,27,35,42,54,56,67] Occasionally, the disease may resemble benign hereditary chorea, myoclonic dystonia, spastic paraparesis and alternating hemiplegia of childhood.[30,37,49,65]

The paroxysmal dyskinetic episodes can have multiple triggers and episodes may occur at nighttime, resulting in prolonged awakenings and sleep fragmentation. This contrasts with what is observed in other forms of paroxysmal dyskinesias.[50] When present, the episodes of nocturnal dyskinesias and perioral twitches are good diagnostic clues.[1,64] Beyond the well-characterized paroxysmal events, some patients with ADCY5-RMD describe fluctuations in the severity of the movement disorder with no clear onset or offset.

Children with ADCY5-RMD may have developmental delays in motor or speech acquisition. Typically, symptoms are non-progressive, with onset in childhood and stabilization post-adolescence. Despite dearth of longitudinal data, life expectancy in ADCY5-RMD patients seems to be unchanged.

In addition to symptom variability, patients with ADCY5-RMD also have variable severity. The degree of disability ranges from mild to severe. Somatic mosaicism can partially account for individuals with a milder phenotype.[35] Patients with an autosomal recessive form of inheritance tend to have a more severe phenotype.[5] Furthermore, the position of the mutation in the ADCY5 protein can influence the phenotype. Patients who have mutations in the C1b domain are more likely to have a mild phenotype, in comparison to those with mutations in the C1a and C2a domain who are more likely to have moderate to severe disorders.[35]

Sequencing of *ADCY5* should be proposed to patients with a phenotype consistent with ADCY5-RMD. Considering the rarity of ADCY5-RMD and its wide phenotypic spectrum, the increasing use of movement disorder gene panels or whole exome/genome sequencing will help to decrease the proportion of undiagnosed cases. Importantly, a significant proportion of patients have mosaicism which require deep sequencing and/or allele-specific polymerase chain reaction (PCR).

The current evidence for therapeutic options for ADCY5-RMD is predominantly based on case series and case reports. In addition, therapies that have provided benefit in some individuals have had disappointing results in others. This could be partly due to the fact that ADCY5-RMD is a heterogenous disorder, with variable phenotypes and potentially both gain or loss of protein function leading to clinical disorders. A recent study demonstrated the striking benefits of caffeine on the paroxysmal and permanent movement disorders, likely through the modulation of the A_{2A} receptor.[42] Consistent with this, istradefylline was beneficial in one patient.[44] There are currently two registered ongoing studies trying to get further insight into the effect and safety of A_{2A} receptor antagonists: caffeine (NCT04469283) and theophylline (DRKS00029154).[61,81] One challenge for the near future could be to determine which A_{2A} antagonist has the best benefit to risk ratio. Benzodiazepines have been shown to be useful for the nocturnal dyskinesias.[5,19,21,23,27,51,55] Propranolol might improve chorea.[30,43,76] Bilateral pallidal stimulation has variable and incomplete effects on the permanent symptoms but can be more effective for the paroxysmal manifestations, including nocturnal paroxysmal dyskinesia.[27,32] When available, this surgical option can be considered particularly if the movement disorder is severe and poorly controlled with pharmacological treatment. However, the results are less impressive compared to other forms of dystonia (eg, DYT-*TOR1A*or DYT-*SGCE*) and efficacy may wane over time.[19,32,45,80]

There is a need to better understand the individual pathogenesis of the disorder, possibly by identifying functional markers of cAMP levels in the striatum. This would allow for tailored therapies that could differ between patients with a gain-of-function and those with loss-of-function variants.

Strengths and Limitations

This is the first scoping review on ADCY5-RMD and provides a summary of the existing literature. However, the existing literature consists mainly of case reports and case series, which are biased towards the reporting of atypical clinical findings and positive experience with treatment. Furthermore, since cases were ascertained by investigators, rather than testing for pathogenic variants in an unbiased manner, there is a risk that the clinical features described in these studies are of those patients with a more severe phenotype. There is therefore a need for larger cohort studies to document the symptoms and progression of this disorder. There is also a need for multi-center randomized controlled trials for medications and DBS for ADCY5-RMD to allow for a better understanding of their effect.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

P.J.M.: 1A, 1B, 1C, 2A, 2B, 3A
C.N.: 1A, 1B, 1C, 2A, 2B, 3A
L.S.: 1A, 3B
R.Y.: 1C, 3B
C.G.: 1A, 3B
A.M.: 1A, 3B
M.C.: 1A, 3B
A.M.: 1A, 3B
S.G.: 1A, 3B
G.G.: 1A, 3B
T.M.P.: 1A, 1B, 2A, 2B, 2C
E.R.: 1A, 1B, 2A, 2B, 2C

Disclosures

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Electronic databases searched, search terms used and number of searches retrieved from each database.

Table S2. Data extraction format.

Table S3. Summary of included studies.

Table S4. Clinical presentations of ADCY5-related movement disorders.