REVIEW ARTICLE

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ADCY5-related dyskinesia — case series with literature review

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ABSTRACT

Introduction. ADCY5-related dyskinesia is a rare neurological disease caused by mutations in the gene encoding the adenylyl cyclase 5 (*ADCY5*) isoform, a protein that plays an important role in intracellular transmission. Variants in *ADCY5* are associated with a spectrum of neurological disease encompassing dyskinesia, chorea, and dystonia.

State of the-art. *ADCY5* mutations result in clinically heterogeneous manifestations which comprise a range of core and less to highly variable symptoms. Due to the heterogeneous nature and difficulty in diagnosis of the disorder, available treatments are highly limited.

Clinical implications. ADCY5-related dyskinesia was reported in 52 individuals in the literature over a five-year period (January 2017 to January 2022). We have listed all the symptoms and their frequency. The most common symptom reported in these patients was dystonia. Over 50% of patients developed dyskinesia and chorea. We report two cases of familial occurrence of symptomatic ADCY5-related dyskinesia. A 45-year-old patient presented with involuntary movements which had been occurring since childhood. The proband's neurological examination revealed dysarthria, involuntary myoclonic twitches, and choreic movements. The patient's 9-year-old son had developed involuntary movements, mainly chorea and dystonia.

Future directions. This paper aims to summarise the recent literature on ADCY5-related neurological disorders and to present a new case of a Polish family with *ADCY5* mutation. Genetic diagnostics are important in the context of possible future targeted treatments.

Keywords: *ADCY5*, dyskinesia, ADCY5-related dyskinesia, chorea

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Introduction

Movement disorders refer to a group of neurological conditions usually caused by damage to the basal ganglia. The pathophysiology of these conditions is still not fully understood. In some cases, genetic factors play a well-established role. Interestingly, the same gene can be responsible for different movement disorders in the same family [1]. Recent research has provided more insight into the molecular nature of such diseases [2–4].

This paper aimed to discuss and summarise the current understanding of a condition determined by the malfunctioning enzyme involved in signalling pathways of the nervous system — the adenylyl cyclase (isoform 5).

Isoform 5 of adenylyl cyclase (*ADCY5*) is a protein belonging to the family of adenylyl cyclases (ACs) — enzymes

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responsible for catalysing the transformation of adenosine triphosphate (ATP) into cyclic adenosine-3', 5'-monophosphate (cAMP). Since cAMP plays a prominent role as a second messenger in cells, mutations in AC-encoding genes result in disrupted downstream signalling [5]. The enzyme is encoded by *ADCY5* gene (OMIM 600293) whose mutations have been reported to cause early-onset hyperkinetic movement disorders collectively described as 'ADCY5-related dyskinesia' — a term which comprises a range of phenotypes, the most common of which include dystonia, chorea and dyskinesia (OMIM 606703, 619647, 619651).

ADCY5 is highly expressed in the brain within the basal ganglia. Specifically, it is the isoform of AC present in striatal medium-sized spiny neurons (MSNs) expressing D1 and D2 dopaminergic receptors, and is responsible for signal transduction regulating their synaptic plasticity [5]. In the striatum, *ADCY5* is the primary factor responsible for integrating signals of the dopaminergic system and post-synaptic projection of received stimuli further into the striatonigral and striatopallidal pathways. Its activity in MSNs is responsible for regulating dopaminergic signalling through the two dopamine receptors — stimulating D1 and inhibiting D2 [6]. Molecular findings by Doyle et al. [7] confirmed that gain-of-function *ADCY5* mutants identified in ADCY5-associated dyskinesias responded with increased enzymatic activity upon stimulation with simultaneous diminished response to inhibition through D2 receptors. These findings also point out that increased cAMP synthesis ultimately resulted in altered cell activity leading to enhanced gene transcription. Such dysregulation favouring overstimulation of ADCY5 ultimately results in distorted movement initiation and control.

The ADCY5 protein has two catalytic cyclase domains (C1 and C2) responsible for ATP binding and hydrolysis [8]. Most mutations occur in these two domains with an implication of enzyme-substrate binding (increased affinity to stimulatory factors) or inter-domain, possibly ligand-independent, interactions affecting the formation of the catalytic site [9]. Mutations affecting function of C1a and C2a catalytic domains are predicted to result in more severe presentations. Somatic mosaicism and C1b-affecting mutations are associated with milder, axially asymptomatic, presentations [10–12]. It has also been found that *ADCY5* mutations are associated with decreased expression of phosphodiesterase 10A — an enzyme responsible for cAMP degradation [13].

Upon binding of the neurotransmitter, the G-protein coupled D1 receptor dissociates its stimulatory α subunit, which later on leads to activation of the adenylyl cyclase protein [2, 3]. The two catalytic domains (C1 and C2) of the membrane-bound adenylyl cyclase are responsible for catalysing the conversion of an ATP molecule into a cAMP molecule in the cytoplasm [4]. The cAMP molecule may thereafter induce a variety of reactions as it binds to, and activates, protein kinase A.

In the *ADCY5* gene, *de novo* mutations and somatic mosaicism are quite common [11, 12]. They are usually inherited in an autosomal dominant way, but cases with a recessive pattern of inheritance have also been reported [10, 14, 15]. The disorder is genetically heterogeneous, with most cases presenting as gain-of-function mutants. Loss-of-function and *ADCY5* haploinsufficiency also occur [9, 16]. The most common mutation hotspot is located on residue arginine 418 of the cytoplasmic domain C1 [9].

In the following sections, we aim to summarise the recent literature on ADCY5-related neurological disorders, and we present a new case of a Polish family with *ADCY5* mutation.

Case series of two different groups of neurological symptoms (dyskinesia and Asperger's syndrome) in two generations of a single family

Clinical characteristics

Case I.1: A 45-year-old woman presented with involuntary movements within the facial region and muscle jerks of her upper limbs which had been occurring since childhood. At the age of two, the patient developed viral encephalitis. Her other significant medical history included depressive disorders, a suicide attempt, arterial hypertension, obesity, and polyarthritis. Neurological examination revealed dysarthria, involuntary myoclonic twitches most pronounced within the facial region, choreic movements of mostly distal upper and lower limbs, and chorea of the tongue. Brain MRI, posturography and transcranial USG were normal. Neuropsychological examination revealed significant difficulty in learning new information, memory extraction, and a weakened ability to focus. The patient's symptoms improved with caffeine. (Supplementary Video 1).

Case II.2: The second patient was the 9-year-old son of Case I.1 (Fig. 1). He had been diagnosed with developmental delay (mainly in gross motor skills) and decreased muscle tone at the age of one. After a few months, he developed involuntary choreic and myoclonic movements involving his face, limbs and trunk. He had been prone to falls due to general motor hyperactivity combined with choreic movements. There had been no response to treatment with piracetam, benzodiazepines and CBD. The patient had been receiving special needs education at school. After the genetic diagnosis was established, caffeine treatment was administered, with a very good response in terms of involuntary movements.

Case II.1: Stepbrother of II.2 (Fig. 1) presented with Asperger's syndrome aged 12 years. He had also transient simple motor tics which resolved spontaneously. No involuntary movements were observed at examination (Supplementary Video 1).

Molecular data

WES was performed for I.1 and II.2, showing movement disorders and identifying a common, heterozygous, mutation in the *ADCY5* gene: c.1253G > A (NM_183357.3), p.Arg-418Gln. WES procedure and data analysis were performed, as described previously in [17]. Molecular findings were

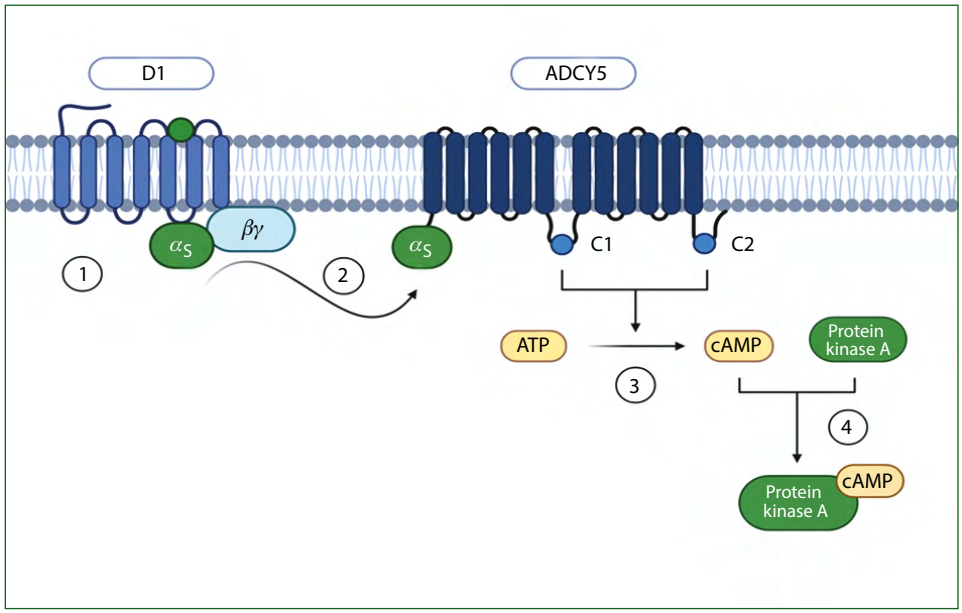

Figure 1. Signalling pathway in which dopamine receptor D1 and ADCY5 are involved [1]

confirmed using the Sanger sequencing method. For II.1 targeting mutation, Sanger sequencing was performed and the presence of mutation in *ADCY5* was excluded.

Material and methods

A search of the PubMed database was performed in January 2022 using the term '*ADCY5*'. 169 articles were found. In our review, we have compiled case reports published between January 2017 and January 2022. We selected all articles published during this period that described cases of patients with *ADCY5* mutations. Experimental and animal studies were excluded. For the final review, we selected 25 articles in which a total of 50 new clinical cases were described. The information regarding the patients' symptoms was collected. The family was examined by a movement disorders specialist.

Results

Herein we describe a two-generational family presenting dominant pattern of inheritance where two different neurological phenotypes could be observed — movement disorder (I.1, II.2) and neurodevelopmental disorder (II.1). The causative mutation in the gene *ADCY5*, heterozygous missense pathogenic variant p.Arg418Gln, was identified in the patients with movement disorder, but analysis was also performed for the patient with Asperger's syndrome. An *ADCY5* mutation was excluded for him, so two different neurological disorders are presented in the brothers. This analysis was performed because of the clinical variability of *ADCY5* mutations. The clinical phenotype of the disorder is broad and usually includes many neurological symptoms, and also some psychiatric. We have listed all the symptoms and their frequency in Table 1. In the Supplement to Table 1 we have listed all the cases included in this study, including a new case (of our 45-year-old patient). The most common symptom, occurring in 82.7% of patients, was dystonia. The second most common was chorea (65.4% of patients). Over 50% of patients presented dyskinesias (57.7%), speech disorders (53.8%) and delayed motor milestones (53.8%). The incidence of hypotonia and myoclonus was 46.2% and 40.4%, respectively. 19.2% of patients were intellectually disabled. Eye-movement disorders such as impaired vertical eye movement, oculomotor apraxia, and saccades were described in 11.5%. Sleep problems were also a frequently reported symptom, occurring in 28.8% of patients. These varied from restless sleep [18] to recurrent paroxysmal nocturnal hyperkinetic attacks [19] or severe and painful exacerbations of dyskinesias present during sleep [20]. Some patients experienced exacerbations of dyskinesia and chorea during sleep [21, 22], with the severity of the sleep-related movements surpassing by far the mild chorea present during daytime [23]. Nocturnal attacks of generalised dystonia with inconsolable crying were also described [20]. In two clinical cases [20], exacerbations of dystonia became less frequent with age. Severely disturbed sleep architecture with frequent awakenings has also been reported [23]. Therefore, sleep problems are a significant clinical symptom reported by patients with the ADCY-5 mutation (Tab. 1).

The severity of symptoms was triggered by various factors. They were often observed immediately after awakening [23–25]. It was not uncommon that psychological factors such as emotions and stress contributed to the increased frequency of attacks [19, 20, 26, 27]. Some of the patients suffered from psychiatric disorders such as depression, anxiety, and phobias

Table 1. Summary of symptoms of patients with ADCY5-related dyskinesia and their frequency

Symptom	Number of patients (n = 52)
Chorea	34/52 (65.4%)
Myoclonia	21/52 (40.4%)
Dystonia	43/52 (82.7%)
Hypotonia	24/52 (46.2%)
Speech disorders	28/52 (53.8%)
Dyskinesia	30/52 (57.7%)
Intellectual disability	10/52 (19.2%)
Eye-movement disorders	6/52 (11.5%)
Delayed motor milestones	28/52 (53.8%)

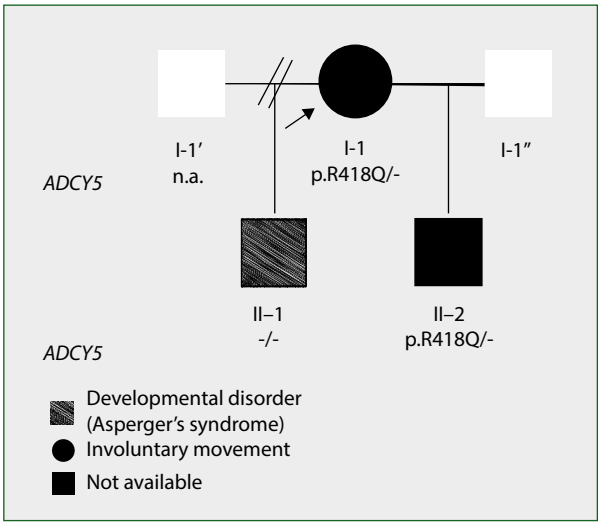

Figure 2. Pedigree of presented family with *ADCY5* mutation

[19, 21, 28]. In some patients, an increase in motor symptoms was observed while walking through narrow passages and while being tired [20]. Exacerbation of symptoms during actions was seen in two patients [23, 26] and intercurrent infection was also a triggering factor in one of them [26]. Language development delay [14, 15, 20] could be partially related to abnormal facial movements or the presence of facial myokymia [18]. Hyperreflexia was reported in three patients [21, 29]. Some patients experienced symptoms such as tremors [15, 30], lower extremity spasticity [30], titubation [31], intermittent retrocollis and episodes of sudden paralysis without loss of consciousness [32].

Nearly all (98%) of the *ADCY5* mutations shown in Table 1 are missense mutations. One of them is a deletion (2%). This data is consistent with data from the literature, which shows that the majority of *ADCY5* gene mutations are missense mutations, although other types of *ADCY5* gene mutations have also been reported [33]. It is possible that the p.Arg418Trp variant is associated with a more severe phenotype; this variant and other mutations at this residue are recurrent, which may indicate that Arg418 is a mutational hotspot [9]. This mutation has high penetration and has also been observed as a *de novo* mutation [34].

However, the observed clinical heterogeneity requires further investigation. as we did not observe a striking genotype-phenotype correlation.

Discussion

Since *ADCY5* mutations were first linked to neurological dysregulation in 2012 by Chen et al. [35], the ADCY5-related spectrum of motor disorders has expanded. *ADCY5* mutations result in clinically heterogeneous manifestations which consist of a range of core and less to highly variable symptoms. Patients most often present with dystonia (which may cause pain), dyskinesia and paroxysmal or episodic hyperkinetic movements (sometimes referred to as non-epileptic 'ballistic bouts') affecting primarily the upper limbs. These can vary substantially in length (from a few minutes to several days) and severity [10].

Due to the heterogeneous nature and observed relative sporadicity of the disorder, available treatments are highly limited. The potential use of deep brain stimulation in the management of nocturnal dyskinetic exacerbations was investigated by de Almeida Marcelino et al. [36]. The authors concluded that the results of their work could pave the way towards successful management of symptoms, as opposed to the dominantly ineffective pharmacological approach.

Carecchio et al. [20] noted that some pharmaceuticals have variable effects in ameliorating the symptoms of the disease in various patients. Individual patients had benefited from acetazolamide or clonazepam treatment. The authors also reported moderate reduction of hyperkinesia in a patient cohort using deep brain stimulation.

Ferrini et al. [9] argued that RNA manipulation is a potential therapeutics-oriented research direction. This should however be preceded by a better understanding of the pathogenesis of the disease on the molecular level, since targeting the specific mechanisms responsible for the symptoms is still unavailable.

Méneret et al. [37] reported improvements in paroxysmal movements in a group of patients in a trial involving caffeine. Patients were administered caffeine doses in the range from 60 to 800 mg per day, and the number of takes varied as well (from one to five). 87% of the cohort reported an improvement in involuntary hyperkinesia of 40% or more. Moreover, improvement in baseline movement disorders and in some concomitant symptoms was observed, while caffeine was found to be well tolerated among patients. Interestingly, a positive impact of istradefylline has also been reported [21].

As can be seen from the Table 1 data, ADCY5-disorder patients may have intellectual disability and delayed milestones. Therefore, it is important to confirm the genetic diagnosis in

patients with various neurological symptoms appearing within one disease. It may have some clinical implications for their treatment or prognosis. This is also why genetic analysis should be performed on siblings/relatives with other neurological symptoms than probands have, so as to differentiate the disease entities because this may well affect treatment. Despite several limitations, our study thus points to a potential research direction.

Although this disease is thought to affect only a small number of patients, due to the development and increasing prevalence of new technologies in diagnostics, such as next generation sequencing, we are now more inclined to expect better detectability and a greater number of patients identified with this disorder in the future. The importance of genetic diagnosis is much more pronounced, in terms of providing the grounds for causal treatment, which is now becoming more tangible. With the increasing availability of genetic testing, future treatments could be delivered more readily to a larger proportion of the population with the disease, and at less advanced stages of the disease.

Therefore, within the development and wider availability of genetic tests lies the promise of early detection followed by a better basis for employment of targeted therapy, both of which could substantially limit the development of the disease, and even prevent its sequelae entirely. Compared to the broad-use therapies employed nowadays discussed in earlier paragraphs, patients suffering from ADCY5-related dysregulation and alike would benefit greatly from direct and selective enzyme pathway or neurosignalling targeting, highlighting further the importance of the development of such procedures and treatments.

Article information

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Conflicts of interest: *The authors declare that they have no conflicts of interest.*

Supplementary materials: *1) Supplementary Video 1 of neurological examination of proband (I.2) and her younger (II.4) son; 2) Supplementary Table to Table 1: A list of all patients included in publication along with their symptoms and publications from which data taken.*

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