REVISTA NEUROCIÊNCIAS

Relato de Caso

ADCY5-related dyskinesia: a treatable inherited neurometabolic disorder

Discinesia relacionada ao ADCY5: um distúrbio neurometabólico hereditário tratável

Discinesia relacionada con ADCY5: un trastorno neurometabólico hereditario tratable

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Resumo

Relato de Caso. Um homem brasileiro de 40 anos procura atendimento por perda de equilíbrio de longa data, distonia e coreoatetose, com pioras paroxísticas episódicas. Sua neuroimagem e a análise de líquor eram normais. A análise quantitativa de ácidos orgânicos na urina, o perfil quantitativo de acilcarnitina plasmática e a análise quantitativa de aminoácidos plasmáticos por cromatografia líquida de alta eficiência estavam todos dentro dos valores de normalidade. O painel de sequenciamento multigênico de segunda geração identificou a variante patogênica heterozigótica c.1252C>T (p.Arg418Trp) no gene ADCY5, fechando diagnóstico de discinesia relacionada ao ADCY5. A associação de cafeína oral e clonazepam proporcionou melhora acentuada dos sintomas motores. **Conclusão**. Este relato de caso acrescenta evidências à segurança e eficácia da cafeína no tratamento de casos geneticamente confirmados de discinesia relacionada ao ADCY5 no contexto de variantes de ganho de função.

Unitermos. Coreoatetose; distonia; ADCY5; doenças metabólicas hereditárias; doenças neurometabólicas; erros inatos do metabolismo

Abstract

Case Report. A 40-year-old Brazilian man presented with long-standing loss of balance, dystonia, and choreoathetosis, with episodic paroxysmal worsening. Neuroimaging and cerebrospinal fluid analysis were both unremarkable. Quantitative urine organic acid analysis, plasma acylcarnitine quantitative profile, and quantitative analysis of plasma amino acids by high performance liquid chromatography were all within normal interval values. Multigene next-generation sequencing panel identified the heterozygous pathogenic variant c.1252C>T (p.Arg418Trp) in the *ADCY5* gene, defining a diagnosis of *ADCY5*-related dyskinesia. Oral caffeine was associated to clonazepam and provided marked improvement of motor symptoms. **Conclusion**. This report adds evidence to the safety and efficacy of caffeine in the treatment of genetically confirmed cases of *ADCY5*-related dyskinesia in the context of gain-of-function variants.

Keywords. Choreoathetosis; dystonia; ADCY5; inherited metabolic disorders; neurometabolic diseases; inborn errors of metabolism

Resumen
Reporte de un caso. Un hombre brasileño de 40 años se presentó con pérdida de equilibrio, distonía y coreoatetosis de larga evolución, con empeoramiento paroxístico episódico. La neuroimagen y el análisis de líquido cefalorraquídeo fueron normales. El análisis cuantitativo de ácidos orgánicos en orina, el perfil cuantitativo de acilcarnitina en plasma y el análisis cuantitativo de cromatografía líquida de alta resolución de aminoácidos plasmáticos estuvieron todos dentro del rango normal. El panel de secuenciación multigénica de próxima segun identificó la variante patógena heterocigota c.1252C>T (p.Arg418Trp) en el gen ADCY5, lo que define un diagnóstico de discinesia relacionada con ADCY5. La asociasión de cafeína oral con clonazepam proporcionó una marcada mejoría en los síntomas motores. **Conclusión**. Este artículo agrega evidencia a la seguridad y eficacia de la cafeína en el tratamiento de casos genéticamente confirmados de discinesia relacionada con ADCY5 en el contexto de variantes de ganancia de función.
Palabras clave. Coreoatetosis; distonía; ADCY5; enfermedades metabólicas hereditarias; enfermedades neurometabólicas; errores innatos del metabolismo

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INTRODUCTION

Inherited neurometabolic disorders represent an expanding and complex group of neurogenetic diseases which can commonly present with complex movement disorders at variable ages of onset[1]. As several of these conditions may be amenable to different specific therapeutic purposes, such as ketogenic diet, vitamin or cofactor supplementation, and diet restrictions, early diagnosis is essential to provide targeted therapies with better outcomes[1]. *ADCY5*-related dyskinesia is a rare autosomal dominant neurogenetic disease, which can present with childhood-onset complex association of hyperkinetic movement disorders[2-4]. Several groups have recommended the use of caffeine as a potential treatment option[3,5]. We present herein and discuss the case of a middle-aged man with long-standing clinical course of

ADCY5-related dyskinesia and marked clinical improvement after caffeine association with benzodiazepine.

CASE REPORT

A 40-year-old Brazilian man started at age 2 years loss of balance and frequent falls. He had almost unremarkable motor and cognitive developmental milestones until age 2 years (CEP: 0825/2018). During childhood, he evolved with stiffness of gait, loss of motor coordination and markedly irregular hyperkinetic movements of the upper and lower limbs, especially during fasting and sleeping and variable symptom relief after breakfast. During his early twenties, he developed dysarthria. In the last years, there was worsening of intensity and length of stiffness in the lower limbs, but there was stability of his involuntary movements of the upper and lower limbs. Patient denied urinary or gastrointestinal complaints. Medical history disclosed a previous episode of aspiration pneumonia during childhood. His parents were not consanguineous, and he had a healthy sister. His previous symptomatic treatments included levodopa, baclofen, carbamazepine and trihexyphenidyl, all of them up to effective dosage and without significant clinical response.

Neurological examination showed marked stiffness of the lower limbs, pseudobulbar affect, intense oral dyskinesias, motor impersistence of the tongue, dystonic posturing of left upper limb and choreoathetosis of both

upper limbs. He had a dystonic gait with evident worsening of choreoathetosis and dystonic posturing while walking. He had no myoclonus or bradykinesia.

Brain MR imaging study with spectroscopy was unremarkable. General serum and urinary lab work-up were unremarkable with no significant metabolic, endocrine, liver and renal function disturbances. Serum and urinary copper and ceruloplasmin levels were normal. Serological testing for viral (HIV, HTLV-I/II, HBV, HCV, CMV, EBV, VZV) and bacterial (VDRL and FTA-Abs) infection were non-reactive. Peripheral blood smear was evaluated three times without the identification of acanthocytes. Quantitative urine organic acid analysis, plasma acylcarnitine quantitative profile, and quantitative analysis of plasma amino acids by high performance liquid chromatography were all within normal interval values. Cerebrospinal fluid analysis was normal. Nerve conduction studies were unremarkable, as well as needle electromyography study. Abdominal ultrasonography was normal. Funduscopic and slit lamp examination were both unremarkable.

Due to the patient's childhood-onset hyperkinetic movement disorder and paroxysmal worsening, a next-generation sequencing-based multigene panel (including genes for inherited neurometabolic disorders, dystonia, choreoathetosis, parkinsonism and neurodegeneration with brain iron accumulation) was requested and revealed the *missense* pathogenic variant c.1252C>T (p.Arg418Trp)

(also known as R418W) in heterozygosis in exon 21 of the *ADCY5* gene (ClinVar: VCV000162090.35). Based upon the confirmatory genetic diagnosis of *ADCY5*-related dyskinesia, clonazepam (up to 3 mg per day) and caffeine 150 mg per day were started with almost 70% of subjective improvement in the rate and intensity of abnormal hyperkinetic movements and nocturnal dyskinetic episodes.

DISCUSSION

ADCY5-related dyskinesia represents a rare and probably underrecognized neurometabolic disorder related to heterozygous pathogenic variants involving the *ADCY5* gene (3q21.1), coding for isoform 5 of adenylyl cyclase involved with cyclic adenosine-3'-5'-monophosphate (cAMP) biosynthesis[3]. It can be rarely associated with homozygous or compound heterozygous variants, presenting with earlier onset presentation, myoclonus, severe global developmental delay, and intellectual disability[4]. ADCY5 is the most common isoform of adenylyl cyclase expressed in GABAergic medium spiny neurons of the striatum, olfactory tubercle, and nucleus accumbens. ADCY5 is involved in several intraneuronal pathways as second messenger and modulates dopaminergic neurotransmission[3]. Gain-of-function effect in *ADCY5* gene, such as with the two most common variants c.2176G>A (A726T) and c.1252C>T (R418W), lead to reduced striatal, cortical, and thalamic inhibition of voluntary and involuntary movements[3].

ADCY5-related dyskinesia must be included in the differential diagnosis of childhood-onset hyperkinetic movement disorders, dominated mainly by choreoathetosis, dystonia and myoclonus[1,2]. Paroxysmal worsening of dystonia and chorea related to sleep, waking up, emotional stress, fasting and fatigue is highly suggestive of heterozygous variants in *ADCY5*, especially in non-progressive presentations with variable facial myokymia and normal cognitive and neuroimaging findings[2,3]. There are no specific serum or cerebrospinal fluid biomarkers which could guide clinicians in their clinical suspicion for *ADCY5*-related movement disorders, resulting in this condition being frequently raised suspicion after extensive negative neuroradiological and laboratory diagnostic work-up[1,3].

Important differential diagnosis in this context includes benign hereditary chorea, Segawa's disease (mainly due to *GCH1* variants), disorders of creatine metabolism, glucose transporter type 1 (*GLUT1*) deficiency syndrome (De Vivo disease), myoclonus dystonia, *PRRT2*-related paroxysmal kinesigenic dyskinesia, cyclic nucleotide phosphodiesterase dysfunction (*PDE2A, PDE10A*), and *ATP1A3*-related disorders[1]. Regarding clinical and genetic correlation, the R418W pathogenic variant has been linked to most de novo cases and commonly with more severe phenotypes. These patients generally have more axial hypotonia, painful dystonia, brisk tendon reflexes, more nocturnal paroxysms, and even cognitive and behavioral disturbances[2,3].

Regarding therapeutic purposes, several strategies have been tried, and conflicting results with variable symptomatic responses have been observed with benzodiazepines, methylphenidate, levodopa, and acetazolamide[2,3]. Even neurosurgical approaches with deep brain stimulation have been performed with good outcomes in some cases[3]. Due to the pathophysiological basis involved in *ADCY5*-related dyskinesia, several authors have proposed the use of caffeine in the treatment of patients with gain-of-function variants[5]. Caffeine is a well-known A2A adenosine receptor antagonist, which could lead to marked reduction of ADCY5 hyperactivation and gain-of-function and provide marked improvement of cAMP levels[5]. Several descriptions in the current literature as well as recently a specific clinical trial have successfully demonstrated significant improvement after treatment with caffeine or during association of benzodiazepines with caffeine[5]. As current literature reported improvement with caffeine and our patient history disclosed improvement after breakfast with coffee consumption, a trial of caffeine was attempted and disclosed very positive outcomes. Our report adds evidence to the safety and efficacy of caffeine in the treatment of genetically confirmed cases of *ADCY5*-related dyskinesias in the context of gain-of-function variants.

CONCLUSION

ADCY5-related movement disorders must be included in the differential diagnosis of patients with early-onset complex neurological phenotypes, mainly with dystonia, choreoathetosis and ataxia, as this condition represents a potentially treatable inherited neurometabolic disorder with oral caffeine. The absence of specific diagnostic biomarkers for these disorders and their normal neuroimaging studies emphasizes that clinicians must be aware about the need to consider broad genetic testing at early stages of diagnostic work-up.

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