Caffeine Significantly Reduces Frequency of Paroxysmal Dyskinesia in a Child with an *ADCY5* Mutation

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Introduction

Mutations in *ADCY5* gene cause early-onset paroxysmal non- kinesigenic dyskinesia (PNKD). Other features may include neurodevelopmental delay and mixed movement disorders such as chorea, athetosis, dystonia, myoclonus affecting the limbs, neck and face. There are currently no clear disease-modifying treatments for ADCY5-related disease, although the role of caffeine is currently being explored.

Case Report

A 7-year-old girl born of non-consanguineous parentage with unremarkable perinatal and family histories, presented with developmental delay and unusual body movements since aged 18 months. She had been experiencing episodic brief, random jerky movements of the upper limbs and fidgety movements of hands suggestive of myoclonus and choreiform movements. She subsequently developed perioral dyskinesia in association with slurring of speech and drooling. The episodes were more noticeable upon awakening in the morning. They worsened with stress and during intercurrent infections. These movements interfered with feeding, writing and dressing skills. Consciousness was never impaired. There was no history of seizures or head drops.

Interictal motor examination showed axial and peripheral hypotonia with normal reflexes and a wide-based gait. She also had "jack in the box" tongue and milkmaid signs.

Extensive investigations including brain MRI scan, EEG and metabolic screening were all non-revealing.

Clinical exome demonstrated likely pathogenic missense variant in the *ADCY5* gene .

A trial of oxcarbazepine (10 mg/kg/day) led to minimal reduction in her symptoms.

She was given caffeine in a dose of 40 mg twice a day in the form of commercial caffeine tablets.

Duration and frequency of paroxysmal episodes before and after treatment with caffeine were noted. We noted significant improvement in her symptoms by 70 to 80% from baseline. No major side effects were encountered.

Discussion

ADCY5 gene encodes adenylyl cyclase which is an important enzyme in the conversion of adenosine triphosphate to cyclic adenosine-3',5'-monophosphate in the striatum where it integrates and controls dopaminergic signaling. Thus, in *ADCY5* mutations, dysregulation of the cAMP pathway leads to reduced inhibitory activity and involuntary hyperkinetic movements (Figure .1).

A reasonable response to treatment with benzodiazepines (clonazepam or clobazam) has been reported in some but with undesirable side effects. Deep brain stimulation (DBS) has also been reported to provide modest improvement however its use is limited by its invasiveness, cost and need for highly specialized expertise.

Caffeine, which is an antagonist of the adenosine A2A receptors that activate ADCY5, has recently been reported to lessen the frequency of PNKD episodes in a few patients with ADCY5 mutations. Caffeine likely inhibits ADCY5 by inhibiting A2A receptors and thus causes reduction of cAMP production. Caffeine thus has been found to reduce the frequency and duration of baseline movement disorders and quality-of-life improvement in patients with gain-of-function mutation and ADCY5 overactivity (Figure. 2).

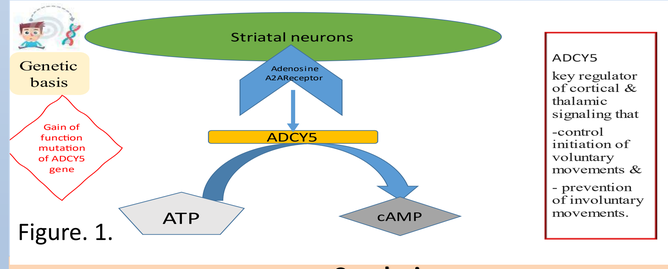

Figure. 1.

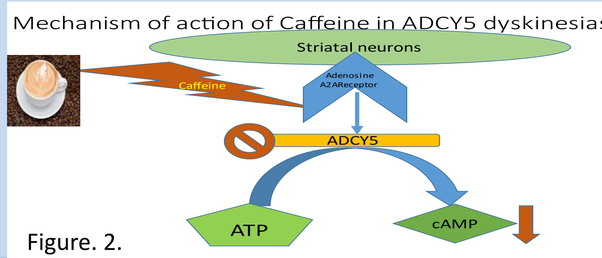

Figure. 2.

Conclusion

- ADCY5-related dyskinesia is one of the many post-synaptic disorders now associated with altered cAMP signaling.
- Caffeine appears to be an effective therapeutic agent in ADCY5-related dyskinesias.
- More research is needed to determine appropriate doses and formulations as well as long term effects.

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References

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