**ADCY5 mutation and Caffeine**

**Discussion**

Mutations in ADCY5 represent a significant genetic cause of early-onset episodic hyperkinetic movements, occurring in isolation or in combination. There are around 60 cases reported worldwide.

ADCY5 gene encodes adenyl cyclase 5 enzyme that converts adenosine triphosphate to cyclic adenosine monophosphate. ADCY5 is highly expressed in the nucleus accumbens and striatum, structures involved in sleep-wake cycle arousal and coordination of movements, respectively.

ADCY5 mutation is reported to be gain of function mutation causing increased adenyl cyclase 5 activity and thus the clinical manifestations.

The onset of symptoms varies from infantile to late adolescent. The inheritance is autosomal dominant, with 100% penetrance.

The initial symptoms include developmental delay, severe axial hypotonia, and dyskinesias. The dyskinetic movements include chorea, athetosis, dystonia, or myoclonus or a combination involving face and limbs which occur as episodic phenomenon or continuous. The severity and frequency of episodic dyskinesia worsens over a time till third decade of life wherein it may completely resolve or become constant. The less common phenotype includes sleep predominance, chorea predominance, myoclonus‐dystonia predominance, and alternating hemiplegia predominance.

Treatment approaches have included trihexyphenidyl, tetrabenazine, clonazepam, carbamazepine, benzodiazepines, but with limited response and 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. Also DBS has been reported to be ineffective for axial hypotonia.

Recently there have been studies reporting dramatic improvement in the patient symptoms following treatment with Caffeine- both in prevention of episodes and reduction of their duration (efficacy estimated to be around 80%). The rationale underlying this observation is that Caffeine is an antagonist of adenosine A2A receptors (A2AR), which activate Adenyl cyclase5(AC5). Caffeine likely induces AC5 inhibition, and thus reduction of cAMP production, leading to clinical improvement in patients with hyperactivity of this protein.

**Conclusion**

Caffeine appears to be an effective therapeutic agent in ADCY5-related dyskinesias, although reported only in few cases so far. More research is needed to determine appropriate doses and formulations as well as long term effects.

**References:**

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