Efficacy of Zinc Treatment in 2 Cases with Arg209Cys Mutation in GNAO1 Gene

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INTRODUCTION

The GNAO1 gene encodes an alpha subunit of the heterotrimeric guanine nucleotide-binding proteins (G proteins), a large family of signal-transducing molecules. Members of the G protein family have been characterized most extensively on the basis of the alpha subunit, which binds guanine nucleotide, is capable of hydrolyzing GTP, and interacts with specific receptor and effector molecules. (Figure 1) Mutations in GNAO1 speed up GTP uptake and inactivate GTP hydrolysis by Gαo (majör neuronal G protein), resulting inconstitutive GTP binding by the G protein. GNAO1 mutations can cause two fenotypes such as developmental and epileptic encephalopathy 17 and neurodevelopmental disorder with involuntary movements which may result epileptic encephalopathy, seizures, delayed pyschomotor development and treatment resistant involuntary movements including chorea, dystonia and athetosis.

OBJECTIVE

Zinc ions have been identified in Drosophila models to restore GTPase activity and cellular interactions of the encephalopathy mutants, with a negligible effect on wild type Gαo, symptoms may be improved with treatment.

MATERIALS & METHODS

The clinical follow-up and zinc treatment of two patients with Arg209Cys mutation in the GNAO1 were evaluated.

RESULTS

First case had intermittent, generalized involuntary movements which started at age of 2 years old after febrile infection. The GNAO1 mutation was demonstrated at age 8. On this period, the patient was treated with carbamazepine, cannabidiol, tetrabenazine and haloperidol at different times and intervals. It was observed that all drugs reduced involuntary movements when they were administered, but their effectiveness was lost over time, especially with febrile infections.

The patient has been followed up for five months with zinc, which was initiated in addition to haloperidol treatment. It was observed that the involuntary movements, which increasing especially when he was excited, decreased at first, but became more frequent over time and there was no significant change in her speech.

While the case 2 was being followed up with hypotonia and neurodevelopmental retardation, involuntary movements started at the age of 4 years. Patient partially benefited from cannabidiol, valproate, trihexyphenidyl and tetrabenazine treatments. Deep brain stimulation (DBS) was applied to the patient who had severe rhabdomyolysis attack and unstoppable, continuous choreatotic movements during pneumonia infection. The patient has been followed up for six months with zinc, addition to DBS, and no significant improvement was observed in her movements.

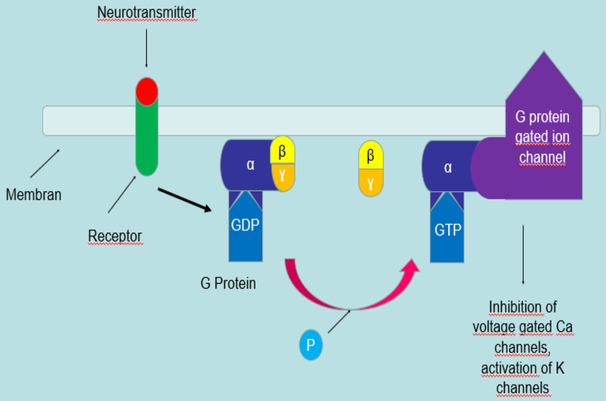

Figure 1: Mechanism of G protein

CONCLUSIONS

Although it's shown that zinc therapy can be effective in the GNAO1 mutation at the molecular level, the clinical efficacy has not been demonstrated.

KEYWORDS

GNAO1 mutation, zinc, movement disorder