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Original Article

Treatment of biotin-responsive basal ganglia disease: Open comparative study between the combination of biotin plus thiamine versus thiamine alone

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ABSTRACT

Objective: To compare the combination of biotin plus thiamine to thiamine alone in treating patients with biotin-responsive basal ganglia disease in an open-label prospective, comparative study.

Methods: twenty patients with genetically proven biotin-responsive basal ganglia disease were enrolled, and received for at least 30 months a combination of biotin plus thiamine or thiamine alone. The outcome measures included duration of the crisis, number of recurrence/admissions, the last neurological examination, the severity of dystonia using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), and the brain MRI findings during the crisis and after 30 months of follow-up.

Results: Ten children with a mean age of 6 years$^{1/2}$ were recruited in the biotin plus thiamine group (group 1) and ten children (6 females and 4 males) with a mean age of 6 years and 2 months were recruited in the thiamine group (group 2). After 2 years of follow-up treatment, 6 of 20 children achieved complete remission, 10 had minimal sequelae in the form of mild dystonia and dysarthria (improvement of the BFMDRS, mean: 80%), and 4 had severe neurologic sequelae. All these 4 patients had delayed diagnosis and management. Regarding outcome measures, both groups have a similar outcome regarding the number of recurrences, the neurologic sequelae (mean BFMDS score between the groups, $p = 0.84$), and the brain MRI findings. The only difference was the duration of the acute crisis: group 1 had faster recovery (2 days), versus 3 days in group 2 ($p = 0.005$).

Conclusion: Our study suggests that over 30 months of treatment, the combination of biotin plus thiamine is not superior to thiamine alone in the treatment of biotin-responsive basal ganglia disease.

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1. Introduction

Biotin-responsive basal ganglia disease (BBGD), also called thiamine transporter-2 deficiency (hTHTR2, OMIM#607483), is a treatable autosomal recessive disorder caused by mutations in the *SLC19A3* gene, encoding the human thiamine transporter 2.[1,2]

The typical clinical presentation of patients with BBGD is recurrent sub-acute episodes of encephalopathy, often triggered by febrile illness, and characterized by confusion, seizures, dystonia, external ophthalmoplegia, eventually leading to coma, and even death.[3,4] In original reports, these attacks respond extremely well to the early administration of high doses of biotin. Thiamine was not effective.[5] However, recent clinical, experimental, and genetic evidence support a major role of thiamine in the treatment of this disease.[3,4,6,7]

The aim of this study is to compare the combination of biotin plus thiamine to thiamine alone in treating BBGD.

2. Materials and methods

We conducted an open-label, prospective, comparative case series study of patients with genetically proven BBGD for at least a 30-month period at Prince Sultan Military Medical City, Riyadh, Saudi Arabia. All patients have the same mutation in the SLC19A3 gene: c.1264A.G (p.Thr422Ala).

Patients are randomized for treatment either with a combination of biotin (5 mg/kg/day) plus thiamine (40 mg/kg/day), group 1: 10 patients, or thiamine (40 mg/kg/day) alone, group 2: 10 patients.

The outcome measures included duration of the crisis (recovery from the encephalopathy), number of recurrence/admissions during the follow-up period (30 months), the last neurological examination (after 30 months) including the neuropsychological profile, and the brain MRI findings during the crisis and after 30 months of follow-up. The severity of dystonia was evaluated at baseline and 12 and 30 months post-treatment using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).[8] The clinically relevant difference for BFMDRS was set at 20% or more, in analogy to previous studies of secondary dystonia.[9] Mean differences between the BFMDRS scores and the days of recover from the encephalopathic episode between the two groups of patients were computed using paired sample *t* tests.

Standard protocol approvals, registrations, and patient consents were obtained. The local hospital ethical review committee approved this study.

3. Results

Twenty patients affected by BBGD were identified, and the demographic, clinical, and neuroradiologic findings are shown in Tables 1 and 2. The two groups were similar in term of clinical presentation and Brain MRI findings. Ten children (5 females and 5 males) with a mean age of 6 years$^{1/2}$ were recruited in the thiamine plus biotin group (group 1). Ten children (6 females and 4 males) with a mean age of 6 years and 2 months were recruited in the thiamine group (group 2). All 20 patients presented with acute/subacute encephalopathy and severe disability as indicated by the baseline BFMDRS scores pre-treatment (mean baseline BFMDRS (MS, motor score) = 77, range 64–88).

After 30 months of follow-up treatment, 6 of 20 children achieved complete remission, 10 had minimal sequelae in the form of mild dystonia and dysarthria not interfering with daily life or school activities as demonstrated by the improvement of the BFMDRS (MS) score (mean 80%, range 61–86%), and 4 had severe neurologic sequelae in the form of spastic quadriplegia, developmental delay, and brain atrophy on the brain MRI (Fig. 1). For these all 4 patients, the BFMDRS (MS) failed to demonstrate meaningful change (mean 13%, range 11–16% at 30 months). All these 4 patients had delayed diagnosis and management.

Brain MRI showed, in all patients, resolution of the infra- and supratentorial brain cortex abnormalities, and in the brainstem. However, chronic changes consistent with atrophy and gliosis are identified in the basal ganglia (Fig. 1). In patients with delayed treatment (4 patients), we observed in addition to these basal ganglia changes, atrophic changes in the cortex.

Regarding outcome measures, both groups have a similar outcome regarding the number of recurrences, the neurologic sequelae, and the brain MRI findings. Comparison of pre- and postreatment BFMDS scores revealed improvement in both groups, however, there is no significant difference between group 1 and group 2 (mean improvement: 71.90% in group 1 and 69% in group 2; $p = 0.84$). The only difference was the duration of the acute crisis: group 1 had significantly faster recovery (2 days; 1.80 ± 0.63), versus 3 days (2.90 ± 0.87) in group 2; $p = 0.005$.

4. Discussion

Even if limited to a relatively small group, this comparative cohort study suggests that the combination of biotin and thiamine is not superior to thiamine alone in treating BBGD, with regards to the number of recurrence, the neurologic sequelae or the brain MRI changes. All patients in both groups showed improvement on their BFMDS scores, but there is no statistical significance between the group 1 treated with the combination of biotin plus thiamine and the group 2 treated with thiamine alone. We only observed statistically faster recovery from the acute attack/crisis in the combination group (2 days versus 3 days).

In the original study, Ozand et al. showed that patients responded only to high doses of biotin and not to thiamine.[5] Of note, thiamine only was used for one patient for 3 months' duration without improvement.[5] However, other studies showed that several patients recovered from the acute crisis only after adding thiamine to biotin.[3,10] Furthermore, it has been reported that one-third of patients that were initially responsive to biotin alone subsequently relapsed, but when thiamine was added further improvement was observed, with no further episodes of decompensation.[4] From a genetic point of view, SLC19A3 gene encodes the human thiamine

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