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The effect of vitamin B12 deficiency on the GH-IGF1 axis

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Abstract
Vitamin B12 (B12) deficiency is associated with growth retardation, reduced serum osteocalcin levels, lower bone mineral density, and increased bone fracture risk, yet the underlying mechanisms remain unclear. However, a recent study showed that B12 positively regulates postweaning growth and bone formation via taurine. B12 deficiency causes growth hormone resistance (GH) and IGF1 (Insulin-like growth factor-1) deficiency. In the present study, we aimed to evaluate the effect of B12 deficiency on the axis of GH-IGF1 and serum taurine level. Eighteen children with B12 deficiency (B12 düzeyi <180 pg/ml) who were 2-17 years-old and referred to Pediatric Haematology Unit in Diyarbakir, between June-August 2015, were included. These subjects had also no growth retardation or any chronic disease. Serum growth hormone, IGF1, IGFBP3 (IGF binding protein-3) and taurine levels were measured before and after oral B12 treatment during 1 month (<20 kg 500 mcg/day, >20 kg 1000 mcg/day). The mean age of the 18 subjects (6F/12M) was 8.0±4.8 years-old. The levels of serum B12, growth hormone, IGF1, IGFBP3 and taurine before and after oral B12 treatment were 132.6±28.4 pg/ml vs 655.8±384.4 pg/ml, 1.20±1.98 vs 1.35±1.20 ng/ml, 213.9±185.8 vs 217.8±181.5 ng/ml, 3683.5±1497 vs 3583.5±1207.3ng/ml, 32.7±18.0 vs 41.1±30.4 µmol/L (N:10-170) ($p<0.0001$,$p=0.41$,0.37,0.28 ve 0.31, respectively). The present study did not detect any relation between B12 deficiency and the GH-IGF1 axis. However, there is a need for the studies that are performed in children with more severe and long-term B12 deficiency.

Keywords: Vitamin B12, taurine, growth hormone, IGF1

Introduction

B12 deficiency is associated with growth retardation, decreased osteocalcin levels, low bone mineral density and an increased risk of bone fracture, although the underlying mechanism remains unclear [1-4]. The growth hormone (GH) axis has long been shown by various studies to be responsible for peripubertal growth [5]. However, the factors regulated by GH in the liver are only now beginning to be understood.

Taurine is a semi-essential amino acid not incorporated in the protein structure. It affects growth and metabolism in mammals, and deficiency is therefore often associated with prenatal and postnatal growth retardation [6]. However, its interaction mechanism was unknown until recent years. Roman-Garcia et al. showed in an animal study that this effect of taurine is mediated by B12 in the GH post-receptor pathway [7]. Direct taurine deficiency or indirect deficiency due to a decrease in taurine synthesis in the liver in association with B12 deficiency has been shown to reduce IGF-1 (Insulin-like growth factor-1) production by leading to GH resistance.

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This study was planned in order to investigate the effect of B12 and taurine levels on the GH axis in the region of Diyarbakır, where B12 deficiency is common.

Materyal and Method

Patients referred to the Diyarbakır Children's Diseases Hospital Pediatric Hematology Clinic, Turkey, with B12 deficiency in June-August 2015 were included in the study. Twenty-nine of these patients, with B12 levels <180 pg/ml, with normal growth-development and physical examination findings and no additional disease aged 2-17 years were enrolled. Patients with further problems in routine parameters other than B12 (glucose, AST, ALT, BUN, creatinine, Na, K, Ca, P, ALP, ferritin, folic acid and complete blood count) were excluded from the study. Patients' serum GH, IGF-1 (Insulin-like growth factor-1), IGFBP3 (IGF binding protein-3) and taurine levels before and after 1-month oral B12 therapy were measured for analysis. B12 therapy was administered orally for 1 month, in dosages of 500 mcg/day for children <20 kg and 1000 mcg/day for those ≥20 kg. Patients who did not complete their treatment or who did not attend on the days specified were excluded, and data for 18 patients were finally evaluated. Verbal and written consent was obtained from all families.

Results

The mean age of the 18 patients in the study (6F,12M) was 8.0±4.8 years. The mean B12 levels at diagnosis were 132.6±28.4 pg/ml, increasing to 655.8±384.4 pg/ml following 1-month oral B12 therapy ($p<0.0001$). Pre- and post-treatment GH levels were 1.20±1.98 vs 1.35±1.20 ng/ml, IGF-1 levels 213.9±185.8 vs 217.8±181.5 ng/ml, IGFBP3 levels 3683.5±1497 vs 3583.5±1207.3ng/ml and taurine levels 32.7±18.0 vs 41.1±30.4 µmol/L (N:10-170 µmol/L), respectively. No statistically significant correlation was observed between pre- and post-treatment GH, IGF-1, IGFBP3 or taurine levels ($p=0.41$, 0.37, 0.28 and 0.31, respectively).

Since only 3 patients had B12 levels <100 pg/ml, no statistical analysis could be performed, but an increase was determined in IGF1 levels (58.9±24 vs 77.7±18.7 ng/ml). No significant difference was observed in terms of gender.

Discussion

This study investigated taurine levels and the GH-IGF1 axis in children with B12 deficiency, and also whether or not there was any increase in these values following B12 therapy. B12 deficiency and therapy were determined to have no effect on taurine levels and the GH-IGF1 axis.

Vitamin B12 is an essential, water-soluble vitamin that regulates several cellular functions. B12 deficiency in humans has to date been linked to growth retardation, low bone mineral density, increased risk of bone fracture and decreased serum osteocalcin levels [1-4]. Although recent studies in particular have clearly shown a decrease in bone mineral density in individuals with vitamin B12 deficiency, the underlying mechanism was unknown. In a recent study, Roman-Garcia et al. created mutant mice (F1) with gastric intrinsic factor (GIF) deficiency and examined the effect of B12 deficiency on both bone metabolism and growth in their offspring, also with GIF deficiency (F2) [7]. Accordingly, there were low but measurable levels of B12 in the F1 mice, and bone density and growth were unaffected, while undetectable levels of B12, decreased bone density and growth retardation were observed in F2 mice. Further studies in F2 mice supported a mechanism whereby vitamin B_{12} deficiency attenuates growth hormone–induced signaling of STAT5 (signal transducer and activator of transcription 5) and diminishes hepatic production of taurine, which in turn lowers the hepatic synthesis of IGF-1. This low IGF-1 indicates the development of resistance to growth hormone, which regulates vitamin B12 dependent taurine synthesis. When taurine therapy alone was administered to the F2 mice with severe B12 deficiency, improvement was observed in both bone density and growth retardation.

In the light of that study, we wished to investigate whether taurine deficiency or GH resistance occurs in children with B12 deficiency, and whether or not there might be a significant increase in their levels after B12 therapy. The fact that taurine deficiency or GH resistance was not determined pre-treatment and that there was no significant increase in their levels post-treatment may be attributed to various causes. One possible cause may be the low number of patients with severe B12 deficiency. An increase was determined in IGF1 levels after B12 therapy in patients with severe B12 deficiency, but statistical analysis could not be performed due to the low number of these patients. Another possible cause is the presence of clinical and laboratory findings of B12 deficiency detected in the F2 mice in the mouse study. In other words, these findings were shown in mice with long-term and much more severe deficiency than the F1 mice, in association with a deficiency that started in the intrauterine period [7]. Since the duration of B12 deficiency in our patients was unknown, this may have affected the lack of significant findings.

In conclusion, this study determined no change in taurine levels of the GH-IGF1 axis in children with B12 deficiency, and observed no increase in levels after B12 therapy. However, performing this study in children with genetic B12 deficiency associated with GIF deficiency and planning an additional GH stimulation test to show the presence of GH resistance might elicit more accurate results.

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