Association between the occurrence of growing pains and vitamin-D deficiency in Indian children aged 3-12 years

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Abstract

Introduction: Growing pains (GP) is a well-recognized entity in children aged 3-12 years. Its diagnosis is based on Peterson criteria. The exact aetiology of GP is not known; however, some studies have linked GP and vitamin-D deficiency.

Objective: To find out the association between occurrence of GP and vitamin-D deficiency (VDD) in Indian children aged 3-12 years.

Method: Children presenting with GP, fulfilling Peterson criteria, were enrolled in the study group, along with an equal number of age and sex matched healthy controls. Analysis of serum calcium, phosphorus, alkaline phosphatase and serum 25-hydroxy-vitamin-D [25(OH)D] levels were done. The results of cases and controls were compared; those children found to have VDD were supplemented with Vitamin-D and response in pain was noted after one month.

Results: Forty five children each were enrolled in the GP and control group. Prevalence of VDD in GP group was (41/45) 91.1% and in control group (26/45) 57.8% [p-value 0.001, RR=7.490; 95%, CI=2.290-24.496]. The mean value of serum calcium, phosphorus, alkaline phosphatase in GP group were 9.50 mg%, 5.15 mg%, 271 IU/L; while in the control group they were 8.84 mg%, 4.72 mg%, 216.2 IU/L respectively. At one month follow-up of GP group, (31/45) 68.9% became asymptomatic while remaining 14 children showed improvement in symptoms.

Conclusions: Children, 3-12 years old, presenting with GP are more likely to have VDD compared to children without GP.

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Introduction

Growing pains (GP) is a well-recognized entity in children usually found in the age group of 3-12 years[1-3]. Its diagnosis remains clinical, based on Peterson criteria comprising bilateral, intermittent, non-articular pain in lower limbs, characteristically occurring in the evening. The physical examination and laboratory parameters are normal, whenever performed[4]. Prevalence of GP ranges from 3 to 50% in different studies[2,5,6]. In the past, the strain of the muscles attached to growing bones and muscle fatigue have been believed to cause GP[1]. Various psychological and familial factors have also been implicated[7]. Even after almost two centuries of its first description in 1823, the aetiology of GP remains poorly understood[5].

Several decades ago, GP was said to be a manifestation of calcium deficiency by Abraham Jacobi[8]. James Dowd, in a blog on vitamin-D, said that "growing pains are a clinical expression of hypovitaminosis D"[8]. There is little knowledge about the association between vitamin-D deficiency (VDD) and GP in children. VDD is widely prevalent in children of Northern India without overt clinical or biochemical evidence of rickets[9,10]. Non availability of vitamin-D fortified food products, vegetarian Indian diets and decreased sun exposure in affluent children may be responsible for the hypovitaminosis-D[10].

Objectives

The primary objective of the study was to compare the VDD status of children presenting with GP with that of healthy controls. Secondary objectives were to compare the mean levels of serum calcium, phosphorus and alkaline phosphatase in both groups.

Method

This cross-sectional study was conducted over a one-year period (January- December 2013) at the out-patient department (OPD) in a tertiary care hospital in Northern India. Ethical clearance was obtained from the Institute Ethics committee before starting the study. Children, 3-12 years old, attending the paediatric OPD with complaints of GP, fulfilling Peterson's diagnostic criteria, were enrolled into our study after obtaining informed

written consent. Children with known organic cause for pain like a rheumatologic disorder, with chronic systemic illnesses and who have received any vitamin-D supplementation in past one year were excluded from the study. An equal number of healthy children (age and sex matched) who were visiting the hospital for routine health check-ups with no history of GP were recruited as controls. After enrolment, a pre-designed questionnaire was filled in by the investigator containing information regarding baseline demographic and socio-cultural details. Clinical characteristics of GP were also recorded. Three millilitre venous blood was collected from enrolled children (cases and controls) for analysis of serum calcium (Ca), phosphorus (P) and alkaline phosphatase (ALP) using kits and calibrators and control from the same supplier [Dimension RxL Max clinical chemistry analyser using specific kits] and serum 25-hydroxy-vitamin-D (25-(OH)D) [Electro-chemiluminescence immunoassay i.e. ECLIA Roche Diagnostics, Germany]. Serum 25-(OH)D level of <20 ng/ml, was considered deficient; a level of 20 to ≤30 ng/ml, insufficient; and a level of >30 ng/ml, was considered optimal[9].

Sample size: Keeping assumptions as VDD among controls 35%, matching 1:1, power 90%, alpha error 5%, sample size was calculated by 45 per group (total 90 children).

Statistical analysis: Descriptive statistics were used to describe baseline variables. The quantitative variables were reported as mean and SD while qualitative variables were reported as proportions. Normal distribution variables were compared by Student's t-test after evaluating equality of variance by Levene's test whereas skewed variables were analysed with an appropriate non-parametric test. A *p*-value (two-tailed) of less than 0.05 was taken as significant. Data was analysed by using SPSS version 14.0, Chicago, Illinois, USA).

Results

This study included a total of 90 children i.e. 45 cases and 45 age and sex matched controls. Mean age in cases and controls was 6.3 years. Regarding sex distribution, the cases and control groups had equal proportions (22 males and 23 females). Baseline parameters were comparable in both groups. GP was mainly in the lower limbs (legs and thighs) in most of the children. It was present mainly during evening or night in 75.6% children. Interventions like local leg massage for relieving this pain was done by the majority i.e. 34 children (75.6%). Other measures were massage and analgesics in four; massage and heat packs in two, analgesics alone in three and no treatment in two children. Behavioural abnormalities were seen in only one child who had aggressive behaviour. An attempt to evaluate any association of GP with hypermobility was made using Beighton Score which uses a 9-point system score for hypermobility[11]. A score of 6 or more indicates hypermobility. In our study 12(26.7%) children in GP group and 8(17.8%) in control group had a score above 6 (p=0.3).

Prevalence of VDD in GP group was 91.1% (41/45) and in the control group, it was 57.8% (26/45) as shown in Table 1.

Nine percent (4/45) of the children in GP group and 20% (9/45) in control group had insufficient levels of 25-(OH)D levels as shown in Figure 1.

Table 1: ***Proportion of children with vitamin-D deficiency (25-(OH)D) in study and control groups***

Growing pains Group *(n=45)* No. (%)	**Control Group *(n=45)* No. (%)**	**RR (95% CI)**	**p value**
41 (91.1)	26 (57.8)	7.490 (2.290 – 24.496)	0.001

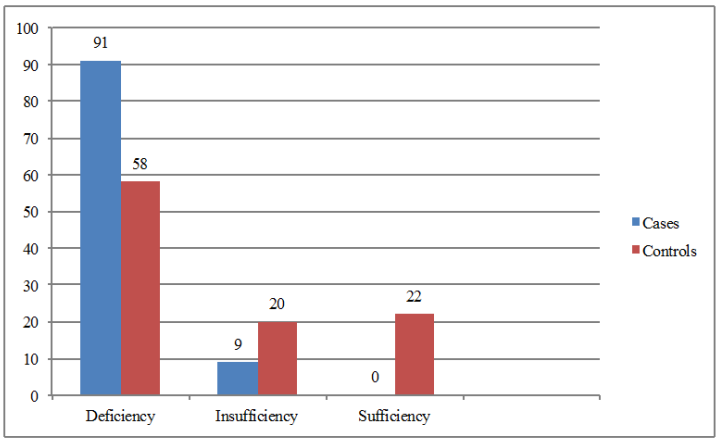

Figure 1: *Vitamin D status of cases (Growing Pains group) and controls*

The mean value of serum calcium in mg/dl among children with GP was 9.5, while in the control group it was 8.8 (p=0.001). The mean value of serum phosphorus in mg/dl among children with GP was 5.1, while in the control group, it was 4.7 (p=0.013). The mean value of serum ALP in U/L among children with GP was 271.9, while in the control group it was 216.2 (p=0.011) as shown in Table 2.

Table-2: ***Comparison of anthropometry and biochemical parameters in study and control groups***

Variable	Growing pains group *(n=45)* mean ± SD	Control group *(n=45)* mean ± SD	*p* value
Age (years)	6.29 ± 2.53	6.29 ± 2.53	1.000
Present weight (kg)	20.00 ± 6.70	18.35 ± 5.66	0.210
Present height (metres)	1.14 ± 0.16	1.11 ± 0.15	0.298
Body mass index	15.07 ± 2.13	14.76 ± 1.72	0.455
Serum calcium (mg/dl) (Normal range=8.8-10.8)	9.50 ± 0.52	8.84 ± 0.91	0.001
Serum phosphorus (mg/dl) (Normal range=3.8-6.5)	5.15 ± 0.84	4.72 ± 0.76	0.013
Serum alkaline phosphatase (U/L) (Normal range=145-420)	271.95 ± 109.04	216.16 ± 92.00	0.011
25(OH) Vitamin D (ng/ml) (Deficiency < 20)	11.47 ± 6.43	18.18 ± 11.54	0.001

The mean value of 25-(OH)D in ng/ml among children with GP was 11.5, while in the control group it was 18.2.

All children with insufficient or low vitamin-D levels were given 600,000 IU oral bolus vitamin-D (*sachet Arachitol® 60,000 IU/sachet*) along with oral calcium supplements (elemental Calcium 50 mg/kg/day) for next 3 months. The children with GP (cases) were interviewed by making a telephone call after one month of vitamin-D bolus supplementation. Out of 45 enrolled children, 31 (68.9%) became asymptomatic while 14 (31.1%) children showed symptomatic improvement in pain. No adverse effect of oral supplementation was reported.

Discussion

In the present study, VDD was significantly commoner in children with GP in comparison with controls. None of the children with GP had vitamin-D levels ≥30 ng/ml. This indicates that children with GP are 7 times more likely to have VDD compared to controls. A study from Pakistan (2011) showed 72% prevalence of VDD in children with GP, similar to our results[12]. Studies from Korea (2015) and Italy (2015) have also shown prevalence of VDD in children with GP to be 57.1% and 43.2% respectively[13,14]. There is a 57.2% prevalence of VDD and a 20% prevalence of vitamin D insufficiency in the control group, indicating widespread prevalence hypovitaminosis-D in children in this region. In another study from same region, 76% of control subjects had VDD or insufficiency[9]. There are other studies from North India showing similar prevalence[10,15-17].

GP in children could be an early manifestation of underlying histological changes in the bone matrix when routine biochemical markers are not markedly abnormal. Low serum concentrations of 25-(OH)D with secondary hyperparathyroidism leads to decreased bone mineral density and resultant osteopenia[18]. With activity, the poorly mineralized bone matrix could hydrate and expands, causing an outward pressure on the periosteum, leading to pain[19]. A study by Uziael Y *et al* showed that in most patients, pain improvement paralleled increase in bone strength[20]. At one month follow-up after treatment of VDD, large majority of children showed clinical improvement in our study, as well. There are studies showing that low vitamin-D status adversely affects bone mass, bone turn-over and muscle strength in children, which could very well contribute to causation of GP in children[21,22].

Regarding the secondary objective of our study, we found that controls had marginally lower mean levels of calcium and phosphorus. This could be a chance finding and did not correlate with the serum alkaline phosphtase levels. Since the majority of these biochemical markers were within normal range, p-value, though statistically significant, may not be of any clinical significance. Irrespective of the wide prevalence of VDD, these biochemical markers were not abnormal in the majority; that signifies the poor sensitivity of them in detecting VDD. Similar findings were also shown in a study from Tehran[15]. Other authors have also reported these biochemical markers of bone turnover to be unreliable even in the setting of secondary hyperparathyroidism[16].

The present study had certain limitations. The sample was drawn from a hospital visiting population and may not reflect the true community prevalence. Secondly, the sample size was small. The temperamental aspects and behavioural disturbances in children could have been more scientifically studied using rating scales or standardized questionnaires. Finally, the cause of GP could be multifactorial and as we only studied one association, a judgement on causation would be incorrect. Furthermore, larger studies would help in confirming the role of vitamin-D supplementation in reducing the incidence of BP.

Conclusions

Children (3-12 years) presenting with GP are more likely to have VDD compared to children without GP.

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