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Article

Perinatal Risk Factors and Genu Valgum Conduce to the Onset of "Growing Pains" in early Childhood

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Abstract: The most prevalent musculoskeletal disorder of childhood with unclear aetiology is Growing Pains (GPs). Anatomic deformities and factors that change bone turnover are implicated in GPs pathophysiology. Perinatal risk factors alter the bone metabolism affecting the bone mineral density and content. The aim of our study was to analyze the relationship between GPs, knock knees and perinatal factors. The examined population consisted of 276 children aged 3-7 years. Among them 10 pairs of dizygotic twins were evaluated. The data were collected by using a combination of semi-structured questionnaires, clinical examinations and medical charts of the children and the obstetric history of the mothers. 78 children presented GPs meeting Peterson's criteria. Genu valgum severity was a significant factor for GPs manifestation and for their increased frequency and intensity. Subsequently, perinatal factors regarding gestational age, Apgar score, head circumference (lower than 33cm) and birth length or weight (smaller than 50 cm and 3000gr, respectively) made a remarkable contribution to the development of GPs. Conversely, antenatal corticosteroid treatment, increased maternal age and maternal smoking during pregnancy were not predictive for the disorder. Our data are potentially supportive for the "bone strength" theory and for the contribution of anatomical disturbances in GPs appearance.

Keywords: Growing pains; genu valgum; perinatal factors; bone metabolism

1. Introduction

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Growing pains (GPs) is the most common form of episodic musculoskeletal pains during childhood. GPs mainly affects children between the ages of 3–12 years [1 –3], but their highest frequency is detected in the age-group of 4 to 6 years [2]. Although GPs were first described by the French physician Duchamp in 1823 [4], their underlying pathophysiological mechanism still remains an enigma. In order to explain their development, various theories have been supported, including the anatomical theory, where lower limb deformities (flat-feet or valgus knee) induce the appearance of pains [5], the nocturnally accelerated bone theory [6], the local overuse syndrome theory [7], the non-inflammatory pain syndrome theory [8] and the hypothesis of early childhood's pain amplification syndrome [9]. Furthermore, a twin family survey [10] provided evidence that GPs appear genetic susceptibility and present genetic association with Restless Leg Syndrome. Currently, many studies focus on the correlation of Growing pains with bone density [7] and with factors affecting paediatric bone metabolism regarding serum levels of vitamin D, or calcium [7] and ω-3 fatty acids intake [11-15]. The bone strength theory is based on the observation that the tibial bone density in children with GPs, as it was measured by quantitive ultrasound, was significantly reduced compared to healthy children [7]. Furthermore, the serum levels of vitamin D3 in GP patients were remarkably low [11-12, 14-15]. Similarly, in the affected children the bone mineral status of the phalanx were low and accompanied by increased serum levels of parathyroid hormone (PTH) whereas the alkaline phosphatase levels were normal [11]. However, the bone strength theory is still subject to further research.

It is recognized from animal based and clinical studies that perinatal risk factors including gestational age [16-17], birth length [17-18], birth weight [18-19] and maternal smoking or ethanol consumption [20] as well as the antenatal use of corticosteroids [17, 21-24], contribute towards alterations in a newborn's bone metabolism having a direct impact on the mineralization of osteoid tissue during infancy. As the skeletal development is strongly related with bone changes during fetal and newborn periods, evaluation of the factors influencing mineral metabolism during early childhood can lead to useful conclusions about skeletal functionality in later life.

The aim of this study is to analyze the possible association between the development and intensity of GPs with perinatal characteristics in children 3 – 7 years old. Moreover, this research examines the possible interaction between the severity of valgus knee deformity and perinatal risk factors in the development of GP in children.

2. Material and Methods

2.1 Study design

This is a retrospective study that was conducted based on the combination of semi-structured questionnaires (a mixture of open and closed questions), clinical examinations and clinical data collected by the medical charts of the children and the obstetric history of the mothers. It took place from January 2014 to January 2015 during the children's visits to the Paediatric department of the co-operated National Primary Care Trust. These visits took place for routine check-ups and vaccinations.Overall 276 children aged 3 to 7 years old, including ten pairs of dizygotic twins, were examined on a daily basis. To determine the correct sample size for our survey, the Cochran's formula was used: $n=Z^2pq/e^2$, where Z is the confidence

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level (1.96), *p* is the variability (0.50), *q* (0.50) and *e* is the precision (7%). Our sample size was thirty per cent larger than the minimum number of participants (n=196) required to ensure accurate results based on the above parameters. The sample was, also, representative of sex, social economic status and geographical distribution including children from local urban, suburban and rural areas as it was based on the social insurance of the participants.

The children's parents or guardians were fully informed about the nature and the aim of the study and written consent was obtained. The study complies with the Helsinki Declaration of 1964.

2.2 Inclusion and exclusion criteria

The inclusion criteria of our research were based on Peterson's [25] definition standards for GPs. These are as follows: recurrent pains in both lower extremities, with duration of up to 72 hrs, usually in the late afternoon or evening, with no arthritic localization or impaired joint mobility, in the absence of rubor, oedema, sensitivity, lesions, infections or other disorders. Exclusion criteria were history of known bone disease or musculoskeletal disorders such as fractures or chronic inflammation, clinical signs of articular disease including swelling, redness, reduced joint range, or trauma. Additionally, children with bone metabolism diseases (i.e. chronic renal syndrome, osteogenesis imperfecta, diastrophic dwarfism) or being under treatment with drugs that increase bone metabolism (i.e. glucocorticoids, anticonvulsants, antiretroviral therapy) were excluded from the study.

2.3 The questionnaire

The questionnaire used included questions concerning the appearance of GP during the year before the children visit to our department, their frequency, and information about their age, sex, ethnicity, medical or orthopaedic history and medication. Wong – Baker Faces Pain Rating Scale (WBFPRS) was used in order to assess pain intensity. WBFPRS is displayed on a horizontal line of six hand-drawn faces that ranged from a smiling face on the left to a crying face on the right, being scored from 0 to ten respectively. We use this scale because its accuracy during the self-report pain intensity in children [26] that develop GP [11] is well documented.

The zygosity of the twin pairs was assessed after applying the twelve-question formula concerning the general similarity between twins, as it was introduced by Jackson et al [27, 28].

Finally, the height and weight of the children were measured and their BMI was calculated. A BMI within the 5^{th} and 95^{th} sex-specific and age-specific percentiles using the Center for Disease Control and Prevention (CDC) revised growth charts was considered normal.

2.4 Tibiofemoral angle and intermalleolar distance

The tibiofemoral (TF) angle and the intermalleolar (IM) distance were measured with a clinical method introduced by Cheng et al [29] that was, also, used by our team as thoroughly described in a previous study [30]. Briefly, the TF angle and the IM distance were measured with children in an upright position ensuring full extension of the knees and neutral rotation

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of the hips using a goniometer and a tape, respectively. The examination was performed by an experienced Paediatric Orthopaedic Surgeon.

2.5 Perinatal factors

The perinatal characteristics were based on the medical charts of the children and the maternal obstetrical history. In specific, we retrieved information regarding gestational age, birth weight, length, head circumference, Apgar score, maternal infection, mode of delivery and use of medication, alcohol or smoking during pregnancy. Gestational age had been estimated from the first day of the last menstrual age. The child with birth weight between the 10th and 90th percentiles for gestational age was called appropriate for gestational age.

Furthermore, data were retrieved for the antenatal use of corticosteroids from the obstetrical files concerning the gestational age at administration of corticosteroids and the number of corticosteroid courses. A complete course of corticosteroid therapy was defined as at least one course of therapy 24 hrs before delivery [31].

2.6 Statistical analysis

The data were initially entered in a Microsoft Excel 2007 spreadsheet and then analyzed statistically using SPSS version 21.0 (IBM Corporation, New York, New York, USA). Initially, the data were summarized using descriptive statistics (mean, SD and 95% confidence interval). Subsequently, the normality of the variables was studied using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Additionally, Levene's test used to assess the equality of variances. Where the distribution of variables was normal the t-test was used, whereas in cases of divergence in the distribution of a variable, we proceeded with the Mann and Whitney –U- test. Due to the limited number of dizygotic twins, the non-parametric Wilcoxon signed-rank test was used. Pearson chi-square test was also used. The level of statistical significance was set to 5% (p=0.05).

3 Results

3.1GPs and demographic characteristics

261 Caucasian children (124 boys and 137 girls) were eligible for inclusion in the study, whereas 15 children were excluded. 78 children (49 boys and 29 girls) met the criteria of Peterson [25] for GPs (Prevalence= 29.88%). The mean age was 5.073±1.217 years (Min: 3, Max: 7.5), the mean weight was 21.24±5.417 kg (Min: 13, Max: 50), the mean height was 113.79±9.580 cm (Min: 91, Max: 139) and the mean BMI value was 16.21±3.534 kg/m^2 (Min: 11.36 Max: 27.85). The children demographics are shown in Table 1. The anthropometric features of the twins group were: the mean age was 4.95±1.10 years (Min: 3, Max: 7), the mean weight was 19.48±4.35 kg (Min: 13.50, Max: 30), the mean height was 110.70±7.62 cm (Min: 97.5, Max: 127) and the mean BMI value was 15.71±1.83 kg/m2 (Min: 12.46 Max: 19.58). The mean age of the affected by GPs children was 5.15±1.21 years (Min: 3, Max: 7), their mean weight was 22.10±6.59 kg (Min: 13.5, Max: 50) while their mean height was 115.13±9.580 cm (Min: 97.5, Max: 139) and their mean BMI value was 16.24±2.64 kg/m2 (Min: 11.42 Max: 27.85).

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Table 1 Demographic characteristics of the study population

Anthropometric characteristics	Mean	Minimum	Maximum	S.D.	Total
Age (years)	5.073	3	7.5	1.2171	N=261
Weight (kg)	21.24	13	50	5.417	N=261
Height (cm)	113.79	91	139	9.580	N=261
BMI (kg/m^2)	16.21	11.36	27.85	3.534	N=261

3.2 GPs and tibiofemoral angle/intermalleolar distance

The mean values, SDs, Min/Max and confidence interval for the anatomic femoral-tibial angles and for the IM distance in both groups are presented in table 2. Increased degree of genu valgum was positively correlated with the development of GPs in children (Table 2). Specifically, TBF angle and IM distance are statistically associated with the appearance of GPs ($p<0.001$ and $p<0.001$, respectively).

Table 2: Descriptive clinical features and statistical analysis of the study participants

Clinical characteristics	With Growing Pains						Without Growing Pains						Statistical significance		
	Mean	Min	Max	S.D.	95% C.I. Lower Bound	95% C.I. Upper Bound	Mean	Min	Max	S.D.	95% C.I Lower Bound	95% C.I Upper Bound	t	Z	*p*
Genu valgum															
TBF angle (degrees)	5.303	0.00	9.00	2.298	4.488	6.118	2.895	0.00	4.00	1.1496	2.341	3.449		-7.07	0.001
IM distance (cm)	3.318	0.0	6.0	1.535	2.774	3.863	1.342	0.0	3.0	0.958	0.880	1.804	-9.61		0.001
Perinatal factors															
Gestational age (weeks)	36.76	28.00	40.00	2.488	35.88	37.64	37.74	34.0	40.0	1.628	36.95	38.52		-4.44	0.001
Corticosteroid treatment (doses)	1.909	1.00	4.00	0.765	1.638	2.180	1.842	1.00	4.00	0.834	1.44	2.24		-0.43	0.570
Apgar score	8.421	6.00	10.0	1.121	7.880	8.961	8.758	6.00	10.0	1.147	8.351	9.164		-2.36	0.018
Birth length (cm)	47.94	40.00	54.00	2.783	46.95	48.92	49.87	45.0	54.0	2.094	48.86	50.88		-5.18	0.001

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Birth weight (gr)	2726.9	1395	3880	578.7	2521.8	2932.2	2983.2	1650	4040	489.01	2747.4	3218.9	3.66	0.001
Head circumference (cm)	33.16	28.00	37.50	1.895	32.45	33.83	34.39	31.4	38.0	1.570	33.63	35.15	3.51	0.001
Maternal age (years)	31.72	21.00	40.00	4.598	30.10	33.36	33.16	26.0	41.0	3.716	31.37	34.95	-0.12	0.907

3.3 GPs and perinatal factors

Statistical analysis revealed that perinatal risk factors are positively correlated with the development of GPs during childhood. In specific, short gestation period, low Apgar score and small birth length or birth weight and head circumference (Table 2) increase the risk of GPs (p< 0.001, p<0.018, p<0.001, p<0.001 and p<0.001, respectively). Interestingly, the risk of GPs development increased when the birth weight of the child was lower than 3000 gr. According to the study's data (Table 3) thirty six out of 187 (19.3%) children suffering from GPs, weighted at birth over 3000 gr while forty two out of seventy four (56.8%) weighted lower than 3000 gr (p<0.001). Similarly (Table 3), the birth head circumference in fifty three out of 219 (24.2%) children suffering from GPs, was greater than 33cm while in twenty five out of forty two (59.5%) was lower than 33 cm (p<0.001). On the contrary, maternal age (p=0.907), maternal smoking during pregnancy (p=0.052) and the antenatal use of corticosteroids (p=0.570) does not seem to be implicated in the development of GPs (Tables 2 and 3).

Table 3: "Growing pains" and their association with perinatal factors

Variable	Present pains (n=78)	Do not present pains (n=183)	Total (n=261)	*p*
I. *Birth weight*				
<3000 gr	n= 42 (56.8%)	n=32 (43.2%)	n=74	0.001
>3000 gr	n=36 (19.3%)	n=151 (80.7%)	n=187	
II. *Head circumference*				
<33 cm	n=25 (59.5%)	n=17 (40.5%)	n=42	0.001
>33 cm	n=53 (24.2%)	n=166 (75.8%)	n=219	
III. *Maternal smoking*				
Non smokers	n=63 (27.8%)	n=164 (72.2%)	n=227	0.052
Smokers	n=15 (44.1%)	n=19 (55.9%)	n=34	

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3.4 Types, frequency and intensity of GPs

We also studied the impact of genu valgum severity and perinatal risk factors on the form and the frequency of GPs. As shown in table 4, IM distance and maternal age are not statistically associated with the type of GPs (Table 4).

Table 4: Statistical correlation between types of "Growing Pains", knock knees and perinatal factors

Type of pain	Mean	S.D.	Std. Error	t	*p*
I. Nocturnal awaking (n=42)					
IM distance (cm)	3.429	1.355	0.209	-0.431	0.668
Birth length (cm)	48.54	2.806	0.433	3.471	0.001
Head circumference (cm)	33.44	1.890	0.291	3.351	0.002
Maternal age (years)	31.61	3.747	0.578	-1.47	0.145
II. Crying (n=36)					
IM distance (cm)	3.472	1.429	0.238	-0.625	0.532
Birth length (cm)	48.62	3.045	0.507	2.368	0.021
Head circumference (cm)	33.39	1.912	0.318	2.928	0.021
Maternal age (years)	31.72	3.739	0.623	-1.517	0.141
III. Pains in both legs (n=51)					
IM distance (cm)	3.324	1.445	0.202	0.378	0.707
Birth length (cm)	48.62	2.571	0.360	4.469	0.001
Head circumference (cm)	33.39	1.573	0.220	5.299	0.001
Maternal age (years)	31.72	4.673	0.654	-2.456	0.017

On the contrary, the perinatal characteristics including small birth length, head circumference and birth weight are strongly correlated with it (Tables 4 and 5). In particular, birth length smaller than 50cm, birth weight lower than 3000gr and head circumference lesser than 33 cm are statistically correlated with nocturnal awaking, crying and pains in both legs (Table 5).

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Table 5: Statistical analysis for the relationship between types of "Growing Pains", perinatal factors and use of corticosteroids

Type of pain	Birth length		*p*	Birth weight		*p*	Head circumference		*p*	Use of corticosteroids		*p*	Total
	<50cm	>50cm		<3000gr	>3000gr		<33cm	>33cm		yes	no		
Nocturnal awaking (n=42)	N=32 (76.2%)	N=10 (23.8%)	0.05	N=31 (73.8%)	N=11 (26.2%)	0.001	N=22 (52.4%)	N=20 (47.6%)	0.001	N=27 (64.3%)	N=15 (35.7%)	0.001	N=42
Crying (n=36)	N=26 (72.2%)	N=10 (27.8%)	0.470	N=28 (77.8%)	N=8 (22.2%)	0.001	N=19 (52.8%)	N=17 (47.2%)	0.001	N=21 (58.3%)	N=15 (41.7%)	0.008	N=36
Pains in both legs (n=51)	N=40 (78.4%)	N=11 (21.6%)	0.003	N=34 (66.7%)	N=17 (33.3%)	0.002	N=23 (45.1%)	N=28 (54.9%)	0.001	N=28 (54.9%)	N=23 (45.1%)	0.002	N=51

Furthermore, the weekly appearance of GPs (Tables 6 and 7) is statistically linked with reduced head circumference (p=0.003) and birth weight (p=0.004), while is not associated with IM distance (p=0.863), birth length (p=0.190) or maternal age (p=0.446). We must underline that although the antenatal administration of corticosteroids was not a contributor factor to the development of GPs, the frequency and the intensity of GPs were elevated in the children had been exposed to dexamethasone (Tables 5 and 7).

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Table 6: Association between the frequency of "Growing Pains", valgus knees and perinatal factors

Frequency of pain	Mean	S.D	Std. Error	Min	Max	F	*p*
I. Weekly (n=19)							
IM distance (cm)	3.368	1.55	0.3563	0	5.5	0.248	0.863
Birth length (cm)	48.70	2.31	0.5295	45	53	1.629	0.190
Head circumference (cm)	33.46	1.75	0.403	31	37	5.223	0.003
Maternal age (years)	31.78	3.49	0.801	27	37	0.900	0.446
II. Monthly (n=33)							
IM distance (cm)	3.333	1.27	0.2216	1	6		
Birth length (cm)	49.06	3.05	0.5304	40	54		
Head circumference (cm)	33.51	1.74	0.3030	28	37		
Maternal age (years)	31.27	4.38	0.7616	23	39		
III. Every three months (n=19)							
IM distance (cm)	3.263	1.48	0.3406	0	6		
Birth length (cm)	50.16	1.56	0.3583	48	53		
Head circumference (cm)	35.03	0.97	0.2220	33.5	37.5		
Maternal age (years)	30.10	4.99	1.1468	21	40		
III. Every six months (n=7)							
IM distance (cm)	3.786	1.38	0.5216	2	6		
Birth length (cm)	50.27	1.05	0.3974	49.3	52		
Head circumference (cm)	34.69	0.76	0.2870	33.5	35.8		
Maternal age (years)	29.14	5.43	2.052	24	40		

Table 7: Association between the frequency of "Growing Pains", Birth weight and perinatal corticosteroid administration

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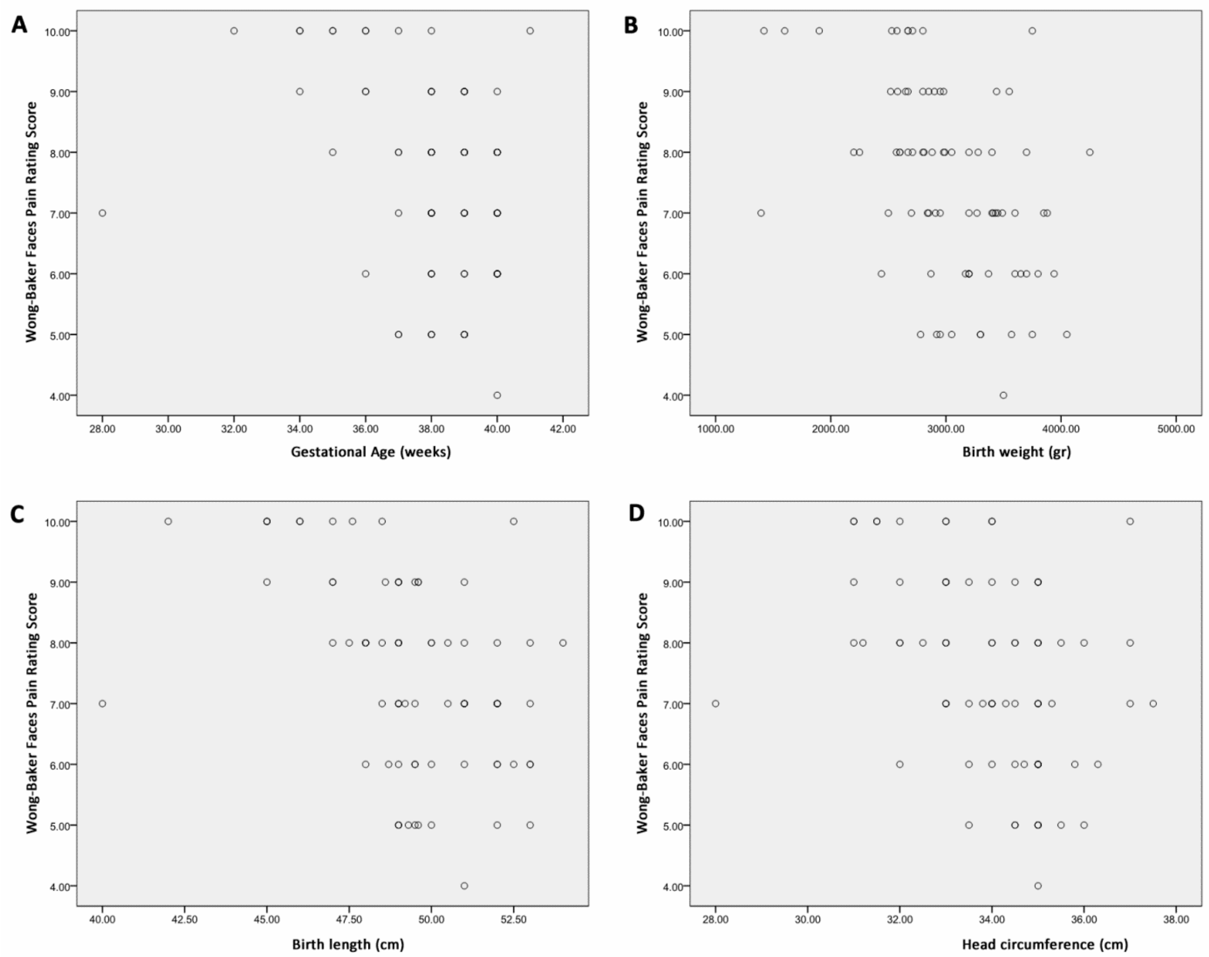
Frequency of pain	Birth weight		*p*	Administration of corticosteroids		*p*	Total
	<3000 gr	>3000 gr	0.004	With corticosteroids	Without corticosteroids	0.001	
Weekly (n=19)	N=14 (73.7%)	N=5 (26.3%)		N=10 (52.6%)	N=9 (47.4%)		N=19
Monthly (n=33)	N=21 (63.6%)	N=12 (36.4%)		N=17 (51.5%)	N=16 (48.5%)		N=33
Every three months (n=19)	N=4 (21.1%)	N=12 (78.9%)		N=6 (31.6%)	N=13 (68.4%)		N=19
Every six months (n=7)	N=3 (42.9%)	N=4 (57.1%)		N=0 (0%)	N=7 (100%)		N=7

Pain intensity was examined using the Wong-Baker score (Image 1). The statistical analysis revealed a correlation between GPs severity and gestational age (p<0.005), birth length (p<0.001), birth weight (p<0.001) and head circumference (p<0.001).

Figure 1: A scatter plot analysis presenting the relationship between pain intensity (Wong-Baker Faces Pain Rating Scale) and gestational age, birth weight, birth length and head circumference



3.5 GPs in dizygotic twins

In our study 10 pairs of dizygotic twins were include and all of the above mentioned variables were examined. Under the assumption that twin pairs share, to a significant extent, environmental and genetic influences, we aim to test if anatomic differences are related with the appearance of GPs. Interestingly, the appearance of GPs in the twins was not affected by the anthropometric characteristics including current weight, height or BMI and the perinatal factors (Table 8). Contrariwise, elevated TBF angle and IM distance (Table 8) are positively associated with the appearance of GPs (p=0.020 and p=0.016, respectively).

Table 8 Statistical analysis of the monozygotic twins clinical characteristics

Clinical characteristics	Present "Growing Pains" (n=9)				Do not present 'Growing Pains" (n=11)				Statistical significance	
	Mean	Min	Max	SD	Mean	Min	Max	SD	Z	*p*
Current weight (kg)	19	13.5	30	5.46	19.86	14	26	3.421	-0.102	0.919
Current height(cm)	108.67	97.50	127	9.052	112.36	102	123	6.169	-1.661	0.097
Current BMI (kg/m^2)	15.81	12.48	19.58	2.302	15.62	12.46	17.19	1.450	-0.663	0.508
TBF angle (degrees)	6.22	3	8	1.481	2.91	1	4	1.044	-2.325	0.020
IM distance (cm)	3.889	2.50	5.5	0.961	1.363	0	3	0.924	-2.409	0.016
Birth length (cm)	47.50	42	52	2.894	49.14	45	51	2.225	-1.074	0.283
Birth weight (kg)	2443.9	1600	2910	417.32	2786	1650	3260	470.49	-1.225	0.221
Head circumference (cm)	33.67	31.50	37.50	1.785	33.65	31.4	36.5	1.568	-0.602	0.574
Apgar score	7.89	6	10	1.616	7.91	6	9	1.136	-0.137	0.891

4. Discussion

The most common cause of musculoskeletal pain during childhood is GPs, which remain largely inexplicable. Despite the fact that GPs are widely considered a benign syndrome and their resolution occur during late childhood, they may have deleterious effects leading many researchers to explore their underlying pathophysiological mechanism. To the best of our knowledge, this is the first study that investigates the association of children's perinatal

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characteristics with the appearance of GPs and examines the correlation of genu valgum severity using clinical methodology, with the frequency and intensity of GPs. However, our research has a number of limitations. First it is retrospective and the data are relying on the information accuracy of the interviewed children or parents. Second, the evaluation of valgus deformity was performed by a clinical method which raises concerns about its reliability and reproducibility. However, the method is well documented and performed by an experienced Paediatric Orthopaedic surgeon. Third, the results are not accompanied by supportive analysis of biological data. Finally, the small number of monozygotic twins did not allow us to draw definite conclusions.

In the present study, GPs prevalence is high corresponding to 29.88% of children aged 3 – 7 years. The reported prevalence differs between various surveys. Evans et al estimated that the frequency of GPs was 36.9% in children 4 to 6 years of age [2]. In a Mediterranean population of children 3 to 12 years old the frequency of the disorder was 24.5% [3] while Oster found that the 15% of school children have occasional limb pain [32]. In a very large British cohort study, but without applying Peterson's criteria for GPs assessment, the referred prevalence was 21.4% [13]. Overall, their prevalence varies from 2.6 to 49.4% [33]. Differences not only in sample size or age range and definition criteria but also in ethnicity features may explain this discordance.

Anatomical or mechanical factors were always being considered in the research of GPs [33, 34]. The severity of genu valgum is statistically associated with the development of GPs in children while is not correlated with their frequency and their intensity. Additionally, increased IM distance and TBF angle are strongly related with GPs in dizygotic twins. As we assume that dizygotic twins have been sampled from the same gene pool and similar environmental factors act upon them [35], the knee deformity may have a critical contribution in the appearance of the pains. This finding is in agreement with Brenning's observation that anatomical deformities which cause mechanical instability of the lower limbs including scoliosis, pes planus or genu valgum are closely related with GPs [36]. This is also supported by the study of Evans [5] where the correction of the lower extremity malalignment with shoes inserts reduce the frequency and the severity of GPs. Furthermore, the application of customized foot orthoses that control overpronation and decrease the secondary genu valgum of the knee joint in children with overpronated feet, led to significant improvement in pain degree and frequency after 1 and 3 months [37]. On the contrary, in the study of Evans and Scatter although the navicular height was weakly correlated with foot functional indexes, the overall foot posture examination measurements did not reveal any statistical significance with GPs [38].

Perinatal risk factors concerning short gestation period, low Apgar score and head circumference, birth length or weight under 33 cm, 50 cm and 3000gr respectively, were closely related not only with appearance of GPs but with their frequency and magnitude, too. Several studies have shown that whole body Bone Mineral Content (BMC) correlates with gestational age, body length and body weight. Moreover, growth of head circumference in infants found to be synchronized with long bone growth and integrity [39]. Research data suggest that there was a decrease in Bone Mineral Density (BMD) in animals with intrauterine growth restriction [40]. These animals also had reduced serum concentrations of

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Vitamin D during their first twenty weeks of life which is in line with the observations of Monangi et al [41] where the odds of low serum concentrations of Vitamin D was increased 2.6-fold in infants born less than 28 weeks postmenstrual age. Newborns with low birth weight had, also, lower BMC [42]. Similarly, postnatal measurements with quantitative ultrasound confirm that the values of tibial speed of sound are affected by a short gestation period [43]. This is consistent with the results of Kurl et al [17] where in preterm infants detected remarkably lower BMC and BMD than the term group. It is noteworthy that adolescents with idiopathic short stature appeared a reduction in their BMD [44]. Wang et al. reported that very low birth weight infants had reduced bone mass at ages 5 to 10 y, even after adjustment for height, leanmass, or bone area [45], whereas in the same study, short gestation period was correlated with unfavorable skeletal health among prepubertal boys [45]. Predicated on the concept that Vitamin D deficiency [11, 12-15] and BMD [7] are key factors for the development of GPs, we can speculate that the implication of perinatal risk factors in the bone metabolism process may result to the onset of the disorder.

Contrariwise, antenatal corticosteroid treatment, increased maternal age and maternal smoking during pregnancy were not predictive for GPs. Although corticosteroids are implicated in bone metabolism, many studies have failed to show distinct differences in BMC values between dexamethasone infants and controls [17, 46-47]. Furthermore Korakaki et al reported that bone formation serum markers concentration was unaffected or slightly reduced at birth in neonates of mothers treated with corticosteroids compared to control subjects while the bone resorption markers did not differ among the two groups [23]. Furthermore, the bone collagen markers in the newborns exposed to dexamethasone, were restored during the first ten days of life [23]. Based on the above findings we can hypothesize that the antenatal administration of corticosteroids does not affect the onset of GPs due to the minor impact of dexamethasone on bone turnover in infants.

5. Conclusion

The findings of the present study demonstrate that perinatal risk factors can be predictive of the development of GPs. The close association of gestational age, head circumference and birth length or weight with bone turnover could be supportive to the bone strength theory for this disorder, indicating to clinicians a detailed bone monitoring of this subgroup. Furthermore, our results also support the anatomical theory as the degree of genu valgum has a significant effect on the development of GPs, leading to the notion that an orthotic correction of severe valgus deformity may be an efficient intervention for the prevention or the treatment of this condition.

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Conflicts of interest

There are no conflicts of interest.

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