Normal plasma levels of IGF binding protein in Perthes' disease

Follow-up of previous report

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Plasma levels of insulin-like growth factor binding protein-3 (IGFBP-3) were measured in 55 children with Perthes' disease and 55 age- and sex-matched controls. IGFBP-3 values did not differ between the 2 groups and corresponded well to normal values found by others. The IGF I/IGFBP-3 ratio was reduced during the first 2 years of Perthes' disease. Our findings indicate that low levels of circulating IGF I in Perthes' disease, as we have reported previously, are caused neither by altered concentrations of the principal IGF-binding protein, IGFBP-3, nor by an underlying growth hormone deficiency.

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Submitted 92-09-13. Accepted 93-03-06

We have recently published data indicating that, during the first 2 years after the diagnosis of Perthes' disease of the hips, insulin-like growth-factor I (IGF I) plasma-levels are reduced (Neidel et al. 1992). To determine the role of the IGF binding proteins (IGFBPs) in relation to these findings, we extended our study to the measurement of IGFBP-3, the predominant IGFBP in postnatal life (Blum and Ranke 1990).

Patients and methods

Plasma samples were originally obtained from 59 consecutive children with Perthes' disease and from 59 matched controls. After determination of IGF I, 4 matched pairs (ID numbers 29, 39, 40, 55) had to be dropped from the study, since the remaining sample volumes were too small to permit further measurements. Hence, IGFBP-3 could be assayed in 55 children with Perthes' disease (46 boys, 9 girls, mean age 7 [3–14] years), and 55 age- and sex-matched controls, using a specific radioimmunoassay (Blum et al. 1990; Mediagnost, Tübingen, Germany). Circadian levels of IGFBP-3 have been shown to be constant (Jørgensen et al. 1990).

Results

IGFBP-3 plasma levels did not differ between children with Perthes' disease and matched controls (Table 1); in both groups, they increased during the pre- and early pubertal years in an almost identical manner (Figure 1). The IGF I/IGFBP-3 ratio also increased with age in both groups (linear regression analysis: Perthes' group r 0.46, P 0.0005; Control group r 0.40, P 0.003). The IGF I/IGFBP-3 ratio, however, was reduced during the first 2 years after the diagnosis of Perthes' disease (Table 1). No correlation was found between IGFBP-3 plasma-levels and the amount of time between the diagnosis of Perthes' disease and procurement of the plasma sample (r 0.17, P 0.24; linear regression). Nor was the extent of the femoral head necrosis, grouped according to Catterall, correlated with plasma IGFBP-3-levels (r 0.06, P 0.65; Spearman ranks correlation). Restriction of full weight bearing by means of orthoses (which were used by 32 (IGFBP-3), and 36 (IGF I) children at the time of venepuncture, respectively) did not lead to a reduction of IGFBP-3- (P 0.67) or IGF I-plasma-levels (P 0.30; cross-sectional analysis; one-way analysis of variance). We also failed to find any difference in hormone levels between operated and nonoperated on Perthes children.

Table 1 Data (plasma concentrations) of 55 children with Perthes' disease (P) and 55 age- and sex-matched controls (C). Mean and *SEM*. log(IGF I/IGFBP-3) is based on concentrations expressed as weight per volume, not molar; *P*-values (P vs C) are based on Student's *t*-test

	n	IGFBP-3 (μg/mL)	*P*-value	log(IGF I/ IGFBP-3)	*P*-value
All subjects					
Perthes'	55	3.0 *0.12*	0.77	−1.46 *0.03*	0.08
Controls	55	3.1 *0.14*		−1.39 *0.02*	
Within 2 years after diagnosis of Perthes' disease					
Perthes'	44	3.0 *0.12*	0.71	−1.52 *0.03*	0.004
Controls	44	3.0 *0.16*		−1.40 *0.03*	
More than 2 years after diagnosis of Perthes' disease					
Perthes'	11	3.3 *0.42*	0.98	−1.24 *0.05*	0.09
Controls	11	3.3 *0.32*		−1.38 *0.06*	

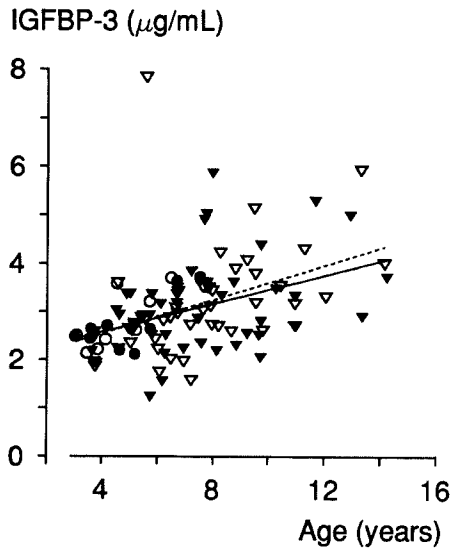

Figure 1. IGFBP-3-plasma concentrations of 55 children with Perthes' disease (▼ ●) and 55 age- and sex-matched controls (▽ ○) in relation to age. ▼ ▽ boys, ● ○ girls. Linear regression lines: Perthes group, solid; control group, dashed. Perthes group: *r* 0.42, *P* 0.0015; control group: *r* 0.43, *P* 0.001 (linear regression analysis).

Discussion

Evidence for a retarded skeletal development in children with Perthes' disease has directed interest towards the metabolism of hormones involved in bone-maturation, most notably IGF I (Burwell 1988). In plasma, nearly all IGF I is bound to specific binding proteins, of which at least 3 different classes have been identified (Ballard et al. 1989). The predominant circulating IGFBP is IGFBP-3, representing more than 95 percent on a molar basis (Blum and Ranke 1990). IGFBP-3 is strongly GH-dependent, and circulates in concentrations equimolar to those of the IGFs, indicating that it is usually fully saturated (Rutanen and Pekonen 1990). Bound IGF I is biologically less active than the free form, IGFBPs therefore presumably play a role in the modulation of IGF-activity.

IGFBP-3 plasma concentrations determined in our children with Perthes' disease and controls correspond well to normal values obtained by others (Blum et al. 1990). In conjunction with our previous results (Neidel et al. 1992), our data provide evidence for reduced levels of IGF I in the presence of normal IGFBP-3-values during the first 2 years after the diagnosis of Perthes' disease. Normal IGFBP-3-levels make an underlying GH-deficiency unlikely, since both the sensitivity and specificity of this parameter in the detection of insufficient GH-secretion have been shown to be 0.95 or better (Blum et al. 1990). Reduced IGF I-levels in affected children were obviously not due to treatment with weight-relieving orthoses, when applied. The combination of moderately reduced IGF I-levels with normal IGFBP-3, on the other hand, seems to be prevalent among children with normal-variant short stature, without GH-deficiency (Cacciari et al. 1985, Blum et al. 1990). Since IGF I as well as the IGF I/IGFBP-3-ratio normally increases during the prepubertal years, a reduction of both parameters could be looked upon as an infantile hormone-pattern which would correspond to the reportedly retarded bone age in children with Perthes' disease. Our data may thus further support the view that Perthes' disease is more common among children whose skeletal maturation is slow.

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