To study the efficacy and safety of growth hormone (GH) therapy in children with Pycnodysostosis

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INTRODUCTION

Pycnodysostosis is a rare recessive condition with mutation in the cathepsin K gene, causing reduction in bone reabsorption resulting in abnormally dense and fragile bones. Characteristic features include deformity of the skull, maxilla causing craniofacial, dental abnormalities with skeletal changes and short stature. Growth hormone therapy has been attempted in a small group of patients with Pycnodysostosis to promote final adult height, however efficacy of its use is debatable*.

OBJECTIVE

To evaluate the efficacy of GH therapy for short stature in three children with Pycnodysostosis.

METHODS

A retrospective analysis of growth data from paediatric outpatient clinic on n=3 children, [2 siblings female (A & B aged 16 and 14yr); and 1 male (C) 15yr]. Both siblings received GH (~3mg/m2 dose) form a private center abroad (Europe), for approximately 4 year period along with puberty blocker injections for ~ 1 to 2 years while on GH. Subject (C) received growth hormone (14.3mcg/kg/day) trial for 4 months at an endocrine center within UK. All patients tested negative for growth hormone deficiency prior to starting GH therapy. Serial anthropometric data pretreatment was compared with that during GH therapy.

RESULTS

1. The pre-treatment height centile for n=3, was < 1st percentile.
2. Height SDS mean (±SD), in (A) pretreatment and end of therapy [– 2.23± 0.2] and [– 2.24± 0.4]; (B) [–2.9 ± 0.2] and [–3.28 ± 0.3] at 4 years; (C) [–3.8 ± 0.2] and [–3.28 ± 0] at 4 months.
3. The height velocity changed from 5.4 (±0.4) to 5.2 (±1.5); 5.5 (±1.5) to 5.9 (±1.4) cm/yr after 4 year treatment in (A) and (B); 5.4 (±2.2) to 5 cm/yr after 4months of treatment in C.
4. IGF1 during GH treatment showed modest rise above normal range.
5. The BMI z score worsened on treatment in (A) +1.67 to +1.93 and (B)+2.8 to 3.19 respectively.
6. There was worsening symptoms of sleep apnea and insulin resistance on GH therapy. There were no symptoms of raised intracranial pressure noted.

Summary of the three cases who received growth hormone therapy

Subject	Data set	Pre-treatment			Growth Hormone therapy (Orange box)							
A	Age (yrs)	6.68	9.86	11.42	12.23	12.43	12.8	13.26	13.83	14.81	15.35	16.17
	Ht SDS	-3.07	-2.81	-2.67	-3.13	-3.29	-3.5	-3.6	-3.73	-3.23	-2.84	-2.9
	Ht Velocity	5.6	5.98	4.85	2.29	6.91	6.59	5.22	3.83	5.93	5.59	5.59
	IGF1 (µg/L)			365		504		784				855
B	Age (yrs)	6.11	8.52	9.54	9.9	10.18	10.36	11.02	11.42	11.91	13.41	13.9
	Ht SDS	-1.82	-2.37	-2.6	-2.53	-2.43	-2.41	-2.5	-1.48	-2.31	-2.62	-3
	Ht Velocity	7.98	5.9	3.64	N/A	7.45	5.62	3.49	5.96	7.34	5.82	3.64
	IGF1 (µg/L)										1094	449
C	Age (yrs)	2.74	4.63	5.68	7.28	7.81	8.77	9.93	10.93	11.93	12.42	14.63
	Ht SDS	-4	-3.9	-3.5	-3.3	-3.5	-3.6	-4	-3.9	-3.7	-3.8	-4.5
	Ht Velocity	N/A	3.82	7	5	2.9	4.02	2.42	3.91	4.63	2.78	2.45
	IGF1 (µg/L)	267	289		380							

Orange box – represent the patient is on growth hormone therapy; Grey- represents off therapy or pre-treatment ; IGF1 in red represent the levels are higher than normal range

CONCLUSION

1. GH therapy failed to show any improvement in growth velocity or height SDS.
2. Increased insulin resistance, weight gain, exponential rise in serum IGF-1 level was seen in 2/3 patients raising concerns about its safety.
3. In contrast to previous report this case series shows no beneficial effect from growth hormone therapy.
4. High IGF1 levels are associated with a greater risk for prostate and breast cancer therefore challenging the potential benefit of GH therapy for treatment of short children with skeletal dysmorphology.

Reference : 1. Soliman et.al; Pycnodysostosis: Clinical, Radiologic, and Endocrine Evaluation and Linear Growth After Growth Hormone Therapy - Metabolism, Vol 50, No 8 (August), 2001.

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