ULNAR MAMMARY SYNDROME – A CASE REPORT

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ABSTRACT

Ulnar mammary syndrome (UMS) is caused by a mutation of T-box transcription factor 3 (TBX3) whose clinical presentation is highly variable .

We present a 14 years 6 months adolescent with concerns short stature in whom investigations were suggestive of growth hormone deficiency and hyogonadotropic hypogonadism. Genetic testing revealed TBX3 gene mutation suggestive of ulnar mammary syndrome.

UMS should be suspected in pateints with subbtle clinical signs suggestive of the condition. Also TBX3 gene should be included among candidate genes for congenital nIHH and idiopathic growth hormone deficiency .

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INTRODUCTION

Ulnar-mammary syndrome (UMS) is an autosomal dominant disorder resulting from TBX3 haploinsufficiency. It typically affects limb, apocrine gland, hair, tooth and genital development . It shows marked intrafamilial and interfamilial variability in phenotypic expression. (1) Despite the lack of association between *TBX3* variants with isolated hypogonadotropic hypogonadism ,signs of hypogonadism, including bilateral cryptorchidism, micropenis and delayed puberty, have been repeatedly reported among patients with UMS . Moreover, the constellation of endocrine manifestations in UMS patients includes short stature, growth hormone deficiency and obesity . However, information on hormonal parameters is scarce to date in UMS patients. Here we report an adolescent who was referred to us for short stature and was found to have hyogonadotropic hypogonadism as well as growth hormone deficiency .

CASE REPORT

A 14 years 6 months old boy was referred for endocrine evaluation of short stature . The patient underwent clinical evaluation, baseline and dynamic hormonal testing, as well as genetic analyses after informed consent from the parents .

He was born term, appropriate for gestational weight to non consanguineous parents with a birth weight of 2.68 kgs , through LSCS . Perinatal history was significant for NICU admission at birth for 10 days for congenital pneumonia. However, there were no episodes of hypoglycemia or prolonged jaundice. At birth he was noted to have bilateral undescended testes and a small penis along with left post axial polydactyly . He underwent underwent bilateral orchiepexy and excision of post axial polydactyly at 1.5years of age . At the time of presentation he denied symptoms of constipation, dry skin, tiredness, nausea or vomiting . His developmental milestones were reportedly normal but he was experiencing academic difficulties . Family history was not significant for pubertal delay , short stature , breast or skeletal abnormalities.

Physical examination showed plagiocephaly, synorphis , thick eyelashes , ankyloglossia and camptodactyly of the right 5th finger. Athropometric measurements revealed that he was short with a height of 149 cms (< −3 SDS on the CDC growth chart) weight of 40.9 kgs (10th to 25th centile) and BMI of 18.4 kgs/m2 (beween 25th to 50th centile on CDC growth chart) . He was prepubertal with bilateral testicular volume of prader 2 mL and stretched penile length of 5cms (-2.5SD) with a width of 1.5 cms . His systemic examination was normal and his sense of smell seemed to be intact.

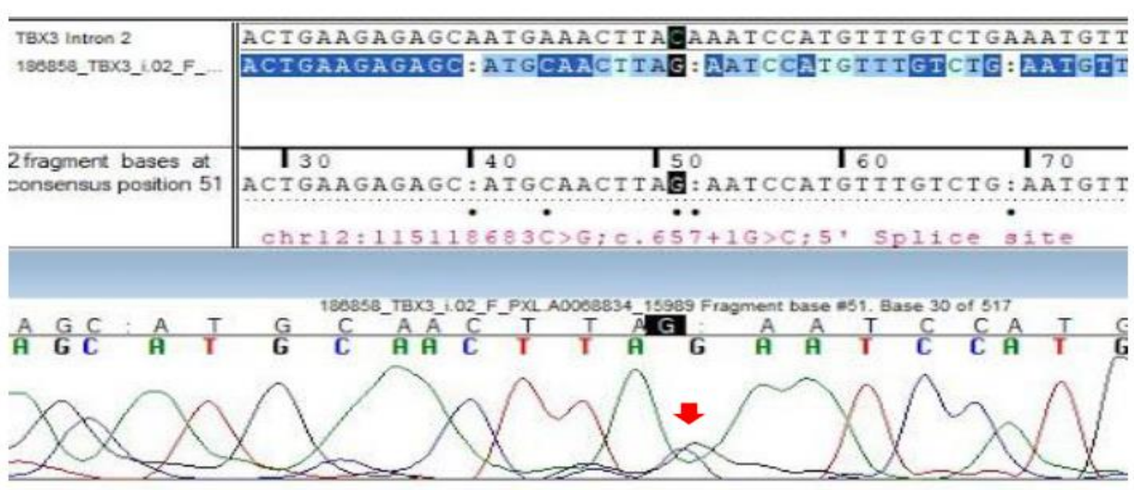
Bone age was 11years 6 months as per Greulich and Pyle atlas . Endocrine evaluation revealed hypogonadotropic hypogonadism and growth hormone deficiency (Table 1) . Karyotype was 46XY . Next generation sequencing revealed a heterozygous 5' splice site variation in intron 2 of the T-box transcription factor 3 (TBX3) gene (chr12:115118683C>G; Depth:158x) that affects the invariant GT donor splice site of exon 2 (c.657 + 1G>C; ENST00000257566) (Figure 1).

He was started on growth hormone and testosterone replacement therapy. His parents were subjected to a clinical examination on follow up and failed to reveal any phenotypic features suggestive of UMS

TABLE 1

INVESTIGATIONS	PATIENT'S VALUE	NORMAL RANGE
IGF-1	160ng/ml	202 to 957 ng/ml
Peak growth hormone Post stimulation with clonidine and glucagon	4.46ng/ml	> 10ng/ml
LH	<0.07micIU/ml	> 0.3 micIU/ml
FSH	1.87 micIU/ml	0.4 to 8.7 mIU/ml
Testosterone	0.25 ng/ml	> 15 ng/ml
Cortisol	16.03 mcg/dl	2.5 to 22.9 mcg/dl
Free T4	8.1	0.92 to 1.57 ng/dl
TSH	3.31 mcIU/ml	0.37 to 6 mcIU/ml

FIGURE 1



Sequence chromatogram and alignment to the reference sequence showing the variation in intron 2 of the TBX3 gene (chr12:115118683C>G; c.657+1G>C; 5' Splice site) detected in heterozygous condition .

DISCUSSION

The *TBX3* gene encodes a member of the T-box family of transcription factors acting as a repressor of target gene expression. TBX3 has a role in the specification of posterior limb mesoderm and in the development of the dorso-ventral limb axis. The same inductive interaction between epithelial tissue and underlying mesenchyme demonstrated for limb buds had been found in breast, tooth and genital development (2). Recently, it has also been reported that Tbx3 functionality is required for the hormone sensing cell lineage in the mammary epithelium (3).
Signs of hypogonadism have been repeatedly reported, but the mechanisms remain elusive. Clinical, biochemical and genetic investigations proved the presence of congenital normosmic IHH (nIHH) associated with growth hormone deficiency in our patient . The associated congenital malformations in our patient were subtle and included ankyloglossia and unilateral post axial polydactyly .

CONCLUSION

1.A diagnosis of UMS should not be dismissed even if not previously recognized in a family member because of the variability in expression.

2 . *TBX3*should be included among candidate genes for congenital nIHH as well as for idiopathic growth hormone deficiency .

REFERENCES

1. Bamshad M, Lin RC, Law DJ, Watkins WC, Krakowiak PA, et al. (1997) Mutations in human TBX3 alter limb, apocrine and genital development in ulnar-mammary syndrome. Nat Genet 16: 311–315 10.1038/ng0797-311
2. Bamshad, M., Root, S., Carey, J. C. Clinical analysis of a large kindred with the Pallister ulnar-mammary syndrome. Am. J. Med. Genet. 65: 325-331, 1996
3. Kunasegaran, Kamini et al. "Transcriptional repressor Tbx3 is required for the hormone-sensing cell lineage in mammary epithelium." *PloS one* vol. 9,10 e110191. 24 Oct. 2014, doi:10.1371/journal.pone.0110191

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