



An Adolescent Girl Presented with Hoarseness of Voice



Ho-chung YAU¹, Yuk-him TAM²

¹ Department of Paediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong

² Division of Paediatric Surgery and Paediatric Urology, Department of Surgery, Prince of Wales Hospital, CUHK, Hong Kong

INTRODUCTION

Androgen insensitivity syndrome (AIS) results from androgen receptor dysfunction and is a common cause of difference of sex development (DSD). This AIS phenotype largely depends on the degree of residual androgen receptor (AR) activity. Here we report an adolescent girl presented with hoarseness of voice.

METHODS

Clinical data was obtained from chart review. Exons and exon-intron junctions of SRY gene were sequenced by the Sanger method. Mutations in SRD5A2 and AR genes were analyzed by whole exome sequencing.

FIGURE 1 Before GnRH Analogue



RESULTS

The girl was born full term vaginally with birth weight 3.380kg. She had stayed in neonatal unit for 3 days for neonatal fever. Physical examination was unremarkable. She had normal-looking female external genitalia. She was discharged after a negative infection screen.

She presented to us again at the age of 11 years with hoarseness of voice. Physical examination revealed normal growth and blood pressure. She had hoarseness of voice with mild laryngeal prominence. She had no goitre and no hirsutism. Pubertal examination showed stage 1 breast, prominent phallus measured 3cm in length and 2cm in width, bilateral palpable gonads in inguinal regions and stage 3 pubic hair. Both labia majora and minora were seen. Urethral opening was seen but vaginal opening was not well seen. Other systemic review was unremarkable.

Extensive investigations were performed for her virilization. Karyotype was 46, XY. SRY gene was present with no mutation detected by Sanger sequencing. Biochemistry showed LH 33.1 IU/L, FSH 61.3 IU/L, oestradiol 26 pmol/L, testosterone 8.3 nmol/L, 17-hydroxyprogesterone 1.9 nmol/L, androstenedione 1.1 nmol/L, AMH 0.39 µg/L, AFP 2 µg/L and b-HCG <1 IU/L. Ultrasonography showed normal adrenal glands, no urogenital anomalies, no uterus and ovary identified and both gonads in inguinal regions. MRI scan confirmed no uterus and ovary identified in pelvis, bilateral undescended testes in inguinal regions and hypoplastic vagina.

Paediatric urologist and paediatric gynaecologist had been consulted. Examination under anaesthesia revealed right gonad at superficial inguinal pouch and left gonad inside inguinal canal. External genitalia favoured female phenotype with normal-looking labia majora and underdeveloped labia minora, separate urethral and vaginal openings at introitus, phallus enlarged measured 4cm in length and 1.6cm in width. Cystoscopy showed normal-looking female type urethra, normal bladder with bilateral ureteric orifices at orthotopic position. Vaginotomy showed blind-ended vagina lined by normal-looking mucosa with length of 4cm, no cervical opening seen.

CONCLUSIONS

PAIS presents with a heterogenous phenotype which can be the result of several different aetiologies. Appropriate endocrine investigations should support the diagnosis of PAIS, but confirmed definitively by identifying an AR gene mutation which is pathogenic.

Whole exome sequencing later revealed no mutation in SRD5A2 gene but a missense mutation c.2591T>A (p.Leu864Gln) in AR gene. This mutation had been found previously in case of complete androgen insensitivity syndrome. The underlying pathology had been thoroughly explained to the parents and the girl. The gender options and subsequent management had been counselled. GnRH analogue was offered to them for adequate time for decision making and defer of surgery during school holiday. 5 months after the treatment, hoarseness of voice improved, and phallus reduced to 3cm in length and 1.3cm in width. Hypothalamic-pituitary gonadal axis was well suppressed with LH <0.30 IU/L, FSH 1.7 IU/L, oestradiol <20 pmol/l and testosterone <0.5 nmol/l.

Bilateral gonadectomy was performed 11 months after treatment. Phallus measured 3cm in length and 1.1cm in width. Histology showed small benign testes, epididymis and adjacent vascular plexuses. Each testis contained immature small seminiferous tubules with mainly small immature Sertoli cells and some spermatogonia. No germ cell tumour or germ cell neoplasia-in-situ was seen. Immunohistochemical studies with human placental ALP, OCT 3/4 and c-KIT did not identify any neoplastic germ cells. Inhibin highlighted the Sertoli cells in the seminiferous tubules. Oral oestradiol replacement 0.25mg daily was started 1 month after operation.

FIGURE 2 After GnRH Analogue



REFERENCES

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