

## Delayed Puberty and Anosmia in CHARGE Syndrome: A Case Report\*

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### Abstract

A 26-year-old female presented to the paediatric clinic at 11 years of age with poor growth. The detection of delayed puberty, anosmia, coloboma and hearing impairment led to a diagnosis of CHARGE syndrome. This was confirmed by a heterogenous *de novo* pathogenic variant c.6955C >T:p.(Arg2319Cys) detected in the CHD7 gene. Detailed assessment, including olfaction, ophthalmic and auditory examination should be part of the evaluation framework in children with delayed growth and puberty.

**Key words:** anosmia, delayed puberty, CHARGE syndrome

### INTRODUCTION

Congenital hypogonadotropic hypogonadism is a disorder of gonadotropin releasing hormone (GnRH) secretion or action, leading to an insufficiency of the hypothalamo-pituitary-gonadal-axis. It can present as lack of mini-puberty during infancy, absence of onset of puberty or arrested puberty, and infertility. The presence of hypogonadotropic hypogonadism and anosmia has been classically associated with Kallmann Syndrome (KS). CHARGE syndrome, which is a differential diagnosis for this clinical entity is less well recognised.

CHARGE syndrome constitutes coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities and ear abnormalities. It has an incidence rate of 1 in 10-15,000 live births and results from loss-of-function variants in the CHD7 gene which is *de novo* in the majority but can also be autosomal dominant in inheritance.<sup>1</sup> The major diagnostic criteria for a diagnosis of CHARGE syndrome proposed by Verloes et al., in 2005 were coloboma, choanal atresia and semi-circular canal agenesis/hypoplasia.<sup>2</sup> Minor criteria proposed were rhombencephalic dysfunction (cranial nerves VII to XII palsies, brainstem dysfunctions), hypothalamo-pituitary dysfunction, heart or oesophageal anomalies, external or middle ear anomalies and intellectual disability.<sup>2</sup> A clinical diagnosis of typical CHARGE syndrome could be made if a patient fulfilled 3 major criteria or 2 major with 2 minor criteria.<sup>2</sup> Since the availability of newer molecular genetic testing techniques for pathogenic CHD7 variants, the phenotypic spectrum of CHARGE syndrome had broadened. New diagnostic criterion proposed by Hale

et al., in 2016 has enabled individuals with fewer and atypical features to be diagnosed with CHARGE syndrome.<sup>3</sup>

### CASE

Our patient was first seen at 11 years old in the general paediatric clinic for poor growth and followed up for possible familial short stature or constitutional delay in growth and puberty (CDGP). She was born at full term, with a birth weight of 2.45 kg. She was always small-sized and grew below the 3<sup>rd</sup> centile since childhood. She had no known medical illnesses. She had previously undergone an operation to correct a left eye squint and lazy eye secondary to an underlying left optic disc coloboma. She had a normal dietary intake. She is an only child of non-consanguineous parents. Her mother had late menarche at 15 years of age and father had late growth spurt after 16 years of age. Her father's height is 169 cm and her mother's height is 150 cm. Mid-parental height is 153 cm. She grew up under normal social circumstances and was good in her studies.

She was referred for paediatric endocrine assessment at age 13 years due to absence of puberty onset and further faltering of her growth. Probing into history revealed that she had no sense of smell since birth. There were no other family members with anosmia or infertility. On physical examination, her weight was 25.6 kg and height was 134.2 cm, both below the 3<sup>rd</sup> centile. She had poor growth velocity of 3.7 cm in the past 1 year and her height had fallen to below her genetic target height range. On physical examination, she was not dysmorphic and there was no cleft lip or palate. She was pre-pubertal with no breast,

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axillary hair or pubic hair development. Other systemic examination was unremarkable.

Her karyotype was 46XX, thus ruling out mosaic Turner syndrome as the cause of her short stature and delayed puberty. Bone age was markedly delayed corresponding to 8 years. Her Insulin-like growth factor 1 (IGF-1) was 172.8µg/L (normal for bone age of 8 years old). A combined pituitary function test revealed isolated hypogonadotropic hypogonadism. Luteinising Hormone (LH) and Follicular Stimulating Hormone (FSH) responses were poor with peak responses of 0.34 IU/L and 2.62 IU/L respectively while serum estradiol was <37 pmol/L (low). Peak growth hormone (GH) was 19.2 mIU/L (normal >20) and peak cortisol was 665 nmol/L (normal >500). She had normal thyroid function tests (thyroid stimulating hormone (TSH) 0.92 mIU/L, free thyroxine (fT4) 13.2 pmol/L) and normal TSH response to TRH (TSH of 9.74 mIU/L at 30 min and 7.72 mIU/L at 60 min). MRI pituitary findings were normal. Nasoscopy was also normal and ruled out occlusion of the nasal passages.

The patient was treated with conjugated estrogen (Premarin) and Norethisterone was added after 3 years. She is presently on Femoston (1/10). She achieved a final height of 152 cm, which approximates her midparental height. She subsequently complained of hearing difficulties at the age of 19 years. Pure tone audiometry revealed bilateral moderate conductive hearing loss (Figure 1). A CT scan of the temporal bones showed absence of all the semi-circular canals bilaterally (Figure 2A). Figure 2B shows the temporal bones of a normal patient used for comparison. On retrospective re-examination, she was found to have a marginally reduced elevation of the right mouth due to a lower right 7<sup>th</sup> cranial nerve palsy. The clinical diagnosis of CHARGE syndrome was made as the patient fulfilled 2 major criteria of CHARGE syndrome i.e., coloboma and absent semi-circular canals and 2 minor criteria i.e., hypogonadotropic hypogonadism and right 7<sup>th</sup> cranial nerve palsy. This was later confirmed by a heterogenous *de novo* pathogenic variant c.6955C >T:p.(Arg2319Cys) detected in the *CHD7* gene by whole exome sequencing.

**DISCUSSION**

Constitutional Delay of Growth and Puberty (CDGP) is an extreme late end of normal pubertal timing and occurs in up to 30% of girls and 65% of boys.<sup>4</sup> Many children with this condition have co-existing familial short stature. It is a far more common cause of delayed puberty compared to congenital hypogonadism, e.g., Kallmann Syndrome (KS) or CHARGE syndrome and often a positive family history of delayed puberty in either parent is present. Girls with no spontaneous puberty beyond the age of 13 years warrant further investigation. In this case, the presence of coloboma, anosmia and hearing impairment pointed to congenital hypogonadism rather than CDGP. Earlier detection of these red flag signs would have enabled earlier diagnosis, earlier screening of other comorbidities and timely pubertal induction at 11-12 years of age.

The multitude of malformations associated with CHARGE syndrome stems from abnormalities in the formation of multipotent migratory neural crest cells in the presence of *CHD7* haploinsufficiency.<sup>5</sup> The *CHD7* gene encodes the Chromodomain Helicase DNA binding

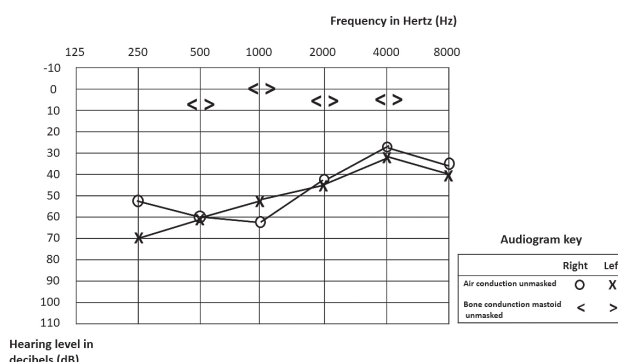


Figure 1. Pure tone audiometry.

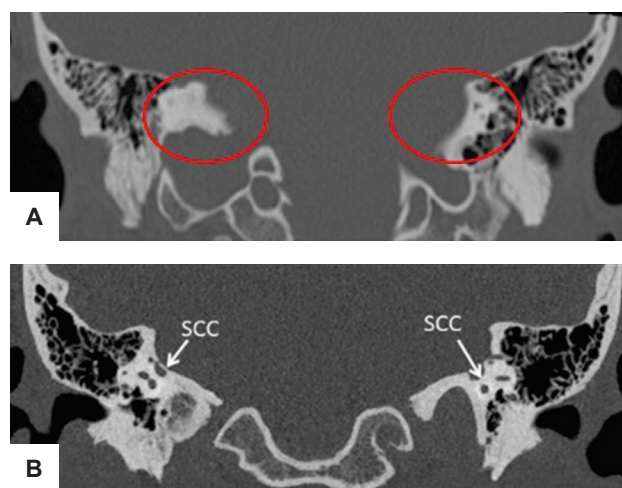


Figure 2. (A) CT temporal bones coronal view showing bilateral absence of all semi-circular canals (SCC); (B) The temporal bones of a normal patient for comparison.

(CHD) protein 7 which is important in regulation of embryonic stem cell pluripotency and remodelling of chromatin.<sup>6</sup> *CHD7* is widely expressed in neural crest derived mesenchyme, undifferentiated neuroepithelium, auditory, nasal and pituitary epithelia, cranial nerves and neural retina.<sup>7</sup> The most common endocrine abnormality found in CHARGE syndrome is hypogonadotropic hypogonadism, occurring in 60-80% of patients.<sup>8</sup> This manifests as micropenis and/or cryptorchidism in boys which is readily detectable at birth. In contrast, girls do not have external genitalia abnormalities. Gonadal defects are only detectable when they fail to enter spontaneous puberty. The frequent coexistence of hypogonadotropic hypogonadism and anosmia in these patients suggests a disruption in the embryonic neuronal migration of the GnRH neurons which share the same pathway with the olfactory neurons to the hypothalamus.

The classical phenotypes of hypogonadotropic hypogonadism and anosmia are both also well recognised features in KS due to defect of the GnRH migration pathway. *CHD7* mutation is not only unique to CHARGE syndrome but has also been reported in both patients with KS and normosmic hypogonadotropic hypogonadism.<sup>9,10</sup> Many of these patients were however found to have extra features of CHARGE syndrome on retrospective reevaluation.<sup>9,10</sup> As the *CHD7* gene affects chromatin structuring and gene expression during embryonic development, it is possible that it could also influence the action or genetic

expression of *KAL1*, *FGFR1*, *FGF8*, *PROKR2* and *PROK2* which are the genes involved in KS.<sup>9</sup> Since Kallmann syndrome is one of the constituent phenotypes seen in CHARGE, some authors recommend performing *CHD7* analysis in KS patients without known mutations when additional CHARGE features are present.<sup>9,10</sup>

The KAL 2 genetic form of KS ie *FGFR1* and *FGF8* gene mutation shares a lot of similar features with CHARGE syndrome as cleft lip or palate, external ear malformation, hearing impairment, corpus callosum agenesis and colobomas can also be present.<sup>11</sup> The most discerning feature which pointed to a diagnosis of CHARGE syndrome rather than KS in this patient was the absence of semi-circular canals which is a feature found in over 95% of patients with CHARGE syndrome but is unusual in other syndromes.<sup>12,13</sup> This patient was also found to have a lower right 7th cranial nerve palsy which is atypical of KS upon re-evaluation. A complete evaluation with dilated eye examination, renal ultrasound, echocardiogram as well as imaging of brain, pituitary gland, temporal bones, olfactory bulbs and choanae has been recommended by The Atlantic Canadian CHARGE syndrome team in patients with suspected CHARGE syndrome for the purpose of diagnosis and medical management.<sup>14</sup> Establishing a diagnosis with genetic testing is also important for genetic counselling regarding reproductive options and recurrence risk. Fertility induction by exogenous gonadotropins or pulsatile GnRH to obtain ovulation is possible in these individuals.<sup>15</sup> It should however be made known to these patients that the risk of having an offspring with CHARGE syndrome is 1/2 (50%) for each pregnancy with an unaffected partner and severity in phenotype is indeterminate due to intra-familial variability seen in this condition.

## CONCLUSION

Detailed clinical assessment, including olfaction, ophthalmic, auditory and ear/teeth/palate examination should be part of the evaluation framework in children with delayed growth and puberty. The presence of non-reproductive anomalies including anosmia, coloboma and hearing defects, are red flag indicators of possible underlying congenital hypogonadism. While KS has an incidence of 1 in 8000 in males, the prevalence is much lower in females, estimated to be 1 in 40000.<sup>11</sup> CHARGE syndrome is a major differential diagnosis for KS, especially in females. Additional CHARGE features should be screened for in patients who present with delayed puberty and anosmia.

### Ethical Consideration

Patient consent was obtained before submission of the manuscript.

### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

The authors declared no conflict of interest.

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