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

Yee Lin Lee,¹ Luke Toh,² Fabian Yap³

¹Department of Paediatrics, Universiti Putra Malaysia
²Department of Diagnostic and Interventional Imaging, KK Women’s and Children’s Hospital, Singapore
³Department of Paediatric Endocrinology, KK Women’s and Children’s Hospital, Singapore

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 hypothalamic-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 CHARGE syndrome gene which is of-function variants in the CHD7 gene which is de novo in the majority but can also be autosomal dominant in inheritance.¹ 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.² 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.² A clinical diagnosis of typical CHARGE syndrome could be made if a patient fulfilled 3 major criteria or 2 major with 2 minor criteria.² 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.³

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 3rd 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 3rd 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,
the presence of CHD7 haploinsufficiency. The CHARGE syndrome stems from abnormalities in the multitude of malformations associated with timely pubertal induction at 11-12 years of age. Diagnosis, earlier screening of other comorbidities and detection of these red flag signs would have enabled earlier of congenital hypogonadism rather than CDGP. Earlier of coloboma, anosmia and hearing impairment pointed warrant further investigation. In this case, the presence of CHARGE syndrome on retrospective reevaluation. Many of these patients were however found to have extra features of CHARGE 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-I) was 172.8 μg/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 7th 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 7th 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. 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 multipotential migratory neural crest cells in the presence of CHD7 haploinsufficiency. The CHD7 gene encodes the Chromodomain Helicase DNA binding (CHD) protein 7 which is important in regulation of embryonic stem cell pluripotency and remodelling of chromatin. CHD7 is widely expressed in neural crest derived mesenchyme, undifferentiated neuroepithelium, auditory, nasal and pituitary epithelia, cranial nerves and neural retina. The most common endocrine abnormality found in CHARGE syndrome is hypogonadotropic hypogonadism, occurring in 60-80% of patients. 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. Many of these patients were however found to have extra features of CHARGE syndrome on retrospective reevaluation. 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, FGFR8, PROKR2 and PRO2 which are the genes involved in KS. 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.9,10

The KAL2 genetic form of KS i.e. FGFR1 and FGFR8 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.11 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.5,13 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 ophthalmic, auditory and ear/teeth/palate examination should be part of the evaluation framework in children with suspected CHARGE syndrome for the purpose of diagnosis and medical management.14 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.15 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, ophthalamic, 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 40000.11 CHARGE syndrome is one of the constituent phenotypes seen in CHARGE, some authors recommend performing CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. Am J Med Genet A. 2016;170A(2):344–54. PMID: 26598800. PMCID: PMC5102387. https://doi.org/10.1002/ajmg.a.37435.


Vol. 35 No. 1 May 2020

www.asean-endocrinejournal.org

Authors are required to accomplish, sign and submit scanned copies of the JAFES Author Form consisting of: (1) Authorship Certification, that authors contributed substantially to the work, that the manuscript has been read and approved by all authors, and that the requirements for authorship have been met by each author; (2) the Author Declaration, that the article represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere, that the article does not infringe or violate any copyrights or intellectual property rights that the author owns or for which he/she has obtained rights/permission; (3) the Author Contribution Disclosure, which lists the specific contributions of authors; and (4) the Author Publishing Agreement which retains author copyright, grants publishing and distribution rights to JAFES, and allows JAFES to apply and enforce an Attribution-Non-Commercial Creative Commons user license. Authors are also required to accomplish, sign, and submit the signed ICMJE form for Disclosure of Potential Conflicts of Interest. For original articles, authors are required to submit a scanned copy of the Ethics Review Approval of their research as well as registration in trial registries as appropriate. For manuscripts reporting data from studies involving animals, authors are required to submit a scanned copy of the Institutional Animal Care and Use Committee approval. For Case Reports or Series, and Images in Endocrinology, consent forms, are required for the publication of information about patients; otherwise, appropriate ethical clearance has been obtained from the institutional review board. Articles and any other material published in the JAFES represent the work of the author(s) and should not be construed to reflect the opinions of the Editors or the Publisher.