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CHARGE Syndrome: an Indonesian case report

Jessica Juan Pramudita^{1,2}, Agustini Utari^{2,3}, Tri Indah Winarni², Sultana MH Faradz²

¹Master of Genetic Counseling, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

²Center for Biomedical Research (CEBIOR) Faculty of Medicine, Diponegoro University, Semarang, Indonesia

³Department of Pediatrics, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

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Abstract

Background: CHARGE syndrome is an autosomal dominant congenital and rare genetic disease. The prevalence of CHARGE syndrome is approximately 1:12,000 births. In the previous study, the *CHD7* gene mutation is responsible in about 2/3 cases of CHARGE syndrome. The syndrome associations consist of C-coloboma of the eyes, H-heart disease, A-atresia of the choanae, R-retarded growth and development, G-genital hypoplasia/genitourinary anomalies and E-ear anomalies and/or hearing loss. All defects are not expected to see in every cases and a different spectrum of associations is seen in most of the cases.

Method: Case was undergone physical examination by experience pediatricians, pedigree construction, and other diagnostic procedure (X-ray, echocardiography, and multi slice computer tomography (MSCT) scan).

Results: A boy aged 2 years 9 months with clinical features with match major and minor criteria of CHARGE syndrome.

Conclusion: Based on clinical diagnostic criteria this case is fulfilling with definite CHARGE syndrome.

Keywords: CHARGE syndrome, *CHD7* gene, clinical criteria

INTRODUCTION

CHARGE syndrome is a genetic disease with autosomal dominant inheritance pattern. This syndrome is known for causing a variety of growth abnormalities (developmental disorder) which affects many organs of the body. The prevalence of this syndrome varies between 1/8,500 to 1/12,000 live births in Europe and Canada,¹ while the prevalence of CHARGE syndrome in Indonesia has not been investigated yet. Based on the clinical phenotype, diagnosis of CHARGE syndrome needs four to six cardinal signs, including both choanal atresia and coloboma iris. Mutation in *CHD7* gene has been found in about 2/3 of the cases of CHARGE syndrome.²⁻⁴ This is why, even today, about 1/3 of CHARGE patients presenting the clinical criteria of the syndrome, do not have mutation of *CHD7* gene.

CHARGE syndrome is mainly caused by nonsense mutation or frame shift mutation that occurred *de novo* in *CHD7* gene.² The gene encodes a Chromodomain Helicase DNA binding (CHD) protein that plays a role in ATP (Adenosine Tri Phosphate)-dependent chromatin remodeling process. The presence of these *de novo* mutations would result in protein haplo insufficiency leading to the pathogenesis of multiple congenital disorders that appear in the case of CHARGE syndrome.⁵⁻⁷ The molecular abnormalities in patients with CHARGE syndrome can be detected using CGH array (Comparative Genomic Hybridization) technique to identify microdeletions or duplications underlying CHARGE syndrome.⁸

We are publishing this article due to peculiarity of the case and improving awareness physicians to diagnose CHARGE syndrome using clinical diagnostic criteria only.

CASE REPORT

A boy aged 2 years 9 month, was brought to the hospital by his parent, with the chief complaint of

* Corresponding Author:

Agustini Utari

Telp./Fax: +62 24 8412311/+62 24 8454174

Email: agustiniutari@gmail.com

feeding difficulty since newborn period and urged to know the confirmation diagnosis. There was a history of short stature, feeding problems, failure to thrive. Prenatal history, there was no eventful during the pregnancy, delivered spontaneously from G3P3A0 mother aged 36-year-old. His birth weight was 2600 g and there was no family history of the same condition. Parent had brought the child to many doctors but there was no specific diagnosis leading to CHARGE syndrome. Case was the only individual who was affected in this three generation family pedigree (see figure 1). Currently, the case had developmental delayed and failure to thrive.

On the anthropometric measurement, the body weight was 4,3 kg, the length was 64 cm, the height SDS was -8,66 (short stature), the weight for height SDS was -3.09 (severe malnutrition). On the physical examinations, microphthalmia and bulbous atrophy were found on the right eye, iris coloboma on the left eye, hypoplasia and abnormal pinnae on the right and left ear cartilage, small nostril on the right side, and high arched palate (see figure 2). Genitalia examination showed micropenis and no palpable gonads. We also found laryngomalacia type 1 and neurogenic dysphagia in this child. X-ray showed the cardiomegaly and further testing using echocardiography revealed the DORV (Double Outlet Right Ventricle) and severe pulmonary stenosis. On ultrasound examination, showed the horseshoe kidney and no testicles found in the scrotum and inguinal region. Diagnostic of multi slice computer tomography (MSCT) scan cerebral showed suspect arachnoid cyst in sella region and microphthalmia in the right eye. Due to the growth problem and developmental delayed, the thyroid level was assessed and revealed that the child had hypothyroidism.

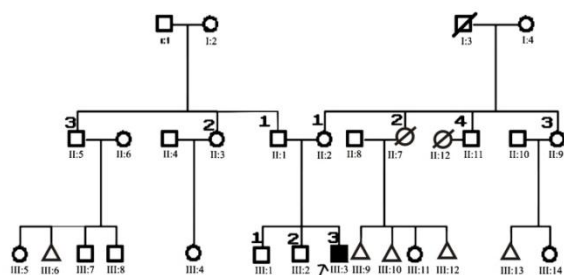


Figure 1. Pedigree of CHARGE syndrome case. The counselee is the only affected individual in three generation pedigree. He has two healthy siblings from healthy parents, thus, the pattern of inheritance is *de novo*.

DISCUSSION

We report a patient with CHARGE syndrome through physical examination, and other diagnostic procedures include radio imaging, echocardiography, and MSCT. Four major diagnostic criteria were found: coloboma iris on the right eyes (unilateral), microphthalmia, cranial nerves dysfunction, and abnormal ear lobes (bilateral). Minor diagnostic criteria was also established such as developmental

delayed, heart defect (severe pulmonary stenosis), undescended testicles, micropenis, short stature, laryngomalacia type 1.^{9, 10}



Figure 2. Clinical features of CHARGE syndrome in the case (patient). Microphthalmia on the right eye (A); Small nostril especially on the left side (B); prominent anti-helix discontinuous with antitragus, rudimentary lobe (C); and thin and unfold helix, prominent anti-helix discontinuous with antitragus, and rudimentary lobe (D).

The CHARGE association was first described in 1979 by Hall et al., in 17 children with multiple congenital anomalies who were ascertained by choanal atresia.¹¹ In the same year, Hittner reported this syndrome in 10 children with ocular colobomas and multiple congenital anomalies.¹² Pagon in 1981 first coined the acronym CHARGE association, Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness, anomalies occurring together more frequently than one would expect on the basis of chance.¹³ The original diagnostic criteria required the presence of four out of six of the CHARGE characteristics. Over the past 15 years the specificity of this pattern of malformations has reached the level that many clinicians now consider it to be a recognizable CHARGE syndrome.¹⁴ In our case the pronounced clinical finding was majority matched to those reported criteria, four major and more than three minor criteria.¹³

Laryngomalacia type 1 and neurogenic dysphagia were found in this case. Laryngomalacia type 1 can

be associated with minor diagnostic criteria tracheoesophageal defect that may cause various spectrum presentation includes stridor, feeding related symptoms (failure to thrive), aspiration and airway obstruction.¹⁵ Although, most laryngomalacia will have mild-moderate symptoms and do not need surgical intervention, severe symptoms have to be considered. Neurogenic dysfunction commonly associated with CHARGE syndrome especially with cranial nerve anomalies (glossopharyngeal and/or the vagus nerves dysfunction).^{9, 14} This anomaly associated with feeding difficulties/failure to thrive since birth as one of parents chief complaint in this case, it cause severe malnutrition. Neonates with CHARGE syndrome facing with multiple lives threatening health conditions and feeding problems can exacerbate the situation.^{9, 14}

Almost all cases of CHARGE syndrome are sporadic cases.¹⁶ With regards to a pattern of inheritance, instead of autosomal dominant, this case was *de novo* mutation. Genetic counseling session should be done to inform and educate the family member about the diseases, pattern of inheritance, risk calculation of the diseases, prognosis and treatment options. Health supervision and management of CHARGE syndrome cases are often complex and need comprehensive approach, comprehensive guidelines that propose a regular approach to medical surveillance and management for physicians and multidisciplinary team for individual with CHARGE syndrome will be helpful.¹⁷

CONCLUSION

To our knowledge so far this is the first Indonesian CHARGE syndrome case report. The major and minor criteria of CHARGE syndrome are present in our case. The peculiarity of this case is definite CHARGE syndrome. The cytogenetic and molecular diagnosis testing should be done to confirm diagnosis in this case.

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