CLINICAL AND CYTOGENETIC PROFILES OF PRIMARY AMENORRHEA PATIENTS

Thesis

Submitted to fulfill the assignment and fit-out requisite in passing Post-graduate program majoring Genetics Counseling
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Master of Biomedical Sciences

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BIOMEDICAL SCIENCE POST GRADUATE
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DECLARATION

I hereby declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institution of tertiary education, there are no elements belonging plagiarism forth in Decree No. 17 of 2010. Information derived from the published or unpublished work of others has been acknowledged in the text and a list of reference is given.

Semarang, September 2017

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LIST OF ABBREVIATIONS

AR	: Androgen receptor
AMH	: Anti mullerian hormone
AHC	: Adrenal hyperplasia congenita
ASD	: Atrial septal defect
BMI	: Body mass index
CGD	: Complete gonadal dysgenesis
CHD	: Congenital heart defect
CAIS	: Complete androgen insensitivity syndrome
CAH	: Congenital adrenal hyperplasia
DSD	: Defective of sexual development
EDTA	: Ethylene diamine tetra-acetic acid
HPO	: Hypothalamo-Hypophysial axis
LH	: Luteinizing hormone
FSH	: Follicular stimulating hormone
IHH	: Idiopathic hypo gonadotrophic hypogonadism
MRKH	: Mayer Rokitanski Kuser Hauser syndrome
PA	: Primary amenorrhea
PAIS	: Partial androgen insensitivity syndrome
POI	: Primary ovarian failure
PR	: Prolactin
PS	: Prader stage

PGD : Pure gonadal dysgenesis

MGD : Mixed gonadal dysgenesis

N/A : Not available

TS : Tanner stage

GLOSSARY

Amenorrhea: The absence of menstruation — one or more missed menstrual periods. Female who have missed at least three menstrual periods in a row have amenorrhea.

Complete Gonadal Dysgenesis (CGD): A disorder of sex development (DSD) associated with anomalies in gonadal development that result in the presence of female external and internal genitalia despite the 46,XY karyotype.

Cytogenetic: The branch of genetics that deals with the cellular component, particularly chromosomes, that is associated with heredity

Disorders of sex Development (DSD): A medical conditions refer to congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical5

Gonad: The embryonic sex before differentiation into definitive testis or ovary, A term referring to the female ovaries and the male testes

Hypogonadothrophic-Hypogonadism: Defective gonadal development or function, or both, resulting from inadequate secretion of pituitary gonadotropins

Luteinizing Hormone (LH): A gonadotropin (a hormone that affects the function of the sex organs) that is released by the pituitary gland in response to luteinizing hormone-releasing hormone

Streak gonads: Underdeveloped and dysfunctioning gonads mainly composed of fibrous tissue

Partial Gonadal Dysgenesis (PGD): A disorder of sex development (DSD) p 0kcassociated with anomalies in g=onadal development that results in genital ambiguity of variable degree ranging from almost female phenotype to almost male phenotype in a patient carrying a male 46,XY karyotype

Phenotype: An appearance or characteristic of an individual, which results from the interaction of the person's genetic makeup and his or her environment

Menarche: The first menstrual cycle, or first menstrual bleeding, in females From both social and medical perspectives, it is often considered the central event of female puberty, as it signals the possibility of fertility.

Mixed Gonadal Dysgenesis (MGD): A disorder of sex development (DSD) associated with a numerical sex chromosome abnormality resulting from Y-chromosome mosaicism and leading to abnormal gonadal development.

Follicle Stimulating Hormone (FSH): A hormone produced by the anterior lobe of the pituitary gland that stimulates the growth of the ovum-containing follicles in the ovary and activates sperm-forming cells

Telarche: The onset of secondary (postnatal) breast development usually occurring at the beginning of puberty in females.

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ABSTRACT

Background: Primary amenorrhea is a symptom that can be caused by different disorders such as gonadal, endocrinal, physiological and genetic disorders. The genetic role in primary amenorrhea is significant and cytogenetic analysis in importance to detect the chromosomal abnormalities associated with primary amenorrhea.

Method: We performed a retrospective descriptive study of 79 PA patients, whom referred to molecular and cytogenetic unit of Center For Biomedical Research CEBIOR, in this study we made a scoring system that consists of four scores, score 1 for PA symptom only, score 2 for PA and poor secondary sexual signs, score 3 for PA, poor secondary sexual signs and short stature, score 4 including PA, poor secondary sexual signs, short stature and webbed neck. All the patients had been distributed to match the scores according to their clinical criteria and then confirmed with the karyotype results.

Aim of study: This study aim to provide the clinical and cytogenetic profile of Indonesian primary amenorrhea patients. And to detect the clinical criteria of primary amenorrhea patients and match it with the karyotype results using scoring system.

Results: The karyotype results of 79 patients of PA revealed 55 (69.6%) patients with female karyotype 46,XX, 6 (7.6%) patients with male karyotype 46,XY, 8(10.1%) patients with monosomy X, 3 (3.8%) patients with 45, X/46,XX, 3 (3.8%) patients with Isochromosome 45 X/46, X,iXq. Mosaicism with Y constitution 45,X/46,XY was seen in 2(2.5%) patients, marker chromosome 45,X/46,X+mar2% in one patient (1.3%) and chromosome 1 and X translocation 46,XX,t(1;X)(p34;q25) detected in one(1.3%) patient. Scoring system results showed that all patients with normal karyotype(46,XX/46,XY) matched score 1 and 2 while 17 patients with chromosomal abnormalities matched score 3 and 4, only One patient with mosaic Turner syndrome 45,X(10%)/46,XX(90%) matched score 1.

Conclusion: Turner syndrome was the most common cause of primary amenorrhea which attest the importance of cytogenetic analysis for diagnosis of primary amenorrhea patients. The scoring system need more study to measure the validity and reliability in aim of use as a clinical tool in future.

Key words: Primary amenorrhea, karyotype, clinical examination, score system

ABSTRAK

Latar Belakang: Amenore primer adalah gejala yang disebabkan oleh berbagai kelainan, seperti kelainan gonad, endokrinologis, fisiologis, dan genetik. Peran genetik pada amenore primer sangat penting dan signifikan terkait dengan analisis sitogenetik untuk mendeteksi kelainan kromosom yang berhubungan dengan amenore primer. Penelitian ini bertujuan untuk menganalisis profil klinis dan sitogenetika pada kasus amenore primer.

Metode: Penelitian ini dilakukan dengan penelitian deskriptif retrospektif terhadap 79 kasus amenore primer, dan mengacu pada unit molekuler dan sitogenetika Pusat Penelitian Biomedis CEBIOR. Dalam penelitian ini digunakan sistem penilaian yang terdiri dari empat skor, skor 1 untuk gejala amenore primer, skor 2 untuk amenore primer dan tanda sekunder sekunder yang buruk, skor 3 untuk amenore primer, tanda sekunder sekunder yang buruk dan perawakan pendek, skor 4 untuk amenore primer, tanda-tanda seksual sekunder yang buruk, perawakan pendek dan leher berselubung. Semua kasus telah didistribusikan ke skor berkorelasi sesuai dengan profil klinis mereka dan kemudian dibandingkan dengan hasil kariotipe.

Tujuan penelitian: Penelitian ini bertujuan untuk memberikan profil klinis dan sitogenetika kasus amenore primer pada populasi Indonesia dan untuk mengetahui frekuensi dan jenis kelainan kromosom pada kasus tersebut. Sistem penilaian menggunakan alat klinis untuk membedakan kira-kira kemungkinan hasil karyotip jika terjadi kekurangan fasilitas genetik.

Hasil: Hasil sitogenetik dari 79 kasus amenore primer menunjukkan 55 (69,6%) kasus dengan kasus kariotipe 46, XX dan enam (7,6%) wanita dengan kariotipe 46 laki-laki, XY. Delapan belas (22,8%) kasus dengan kelainan kromosom. Dari sistem penilaian, menunjukkan bahwa semua kasus dengan kariotipe normal dan 2 sindrom Turner mosaik berbohong di bawah skor 1 dan 2 sedangkan semua kasus dengan kelainan kromosom kecuali 2 dibohongi di bawah skor 3 dan 4

Kesimpulan: Sebagai kesimpulan, dapat dikatakan ada korelasi antara membuktikan pentingnya analisis sitogenetika dalam diagnosis amenore primer dan sistem penilaian dapat membantu prediksi adanya abnormalitas kromosom.

Kata kunci: amenore primer, kariotipe, pemeriksaan klinis