Genetics, Hormonal, and Genital Features of Congenital Adrenal Hyperplasia Patients In Semarang

Submitted to fulfil the assignment
And fit-out requisite in passing
Undergraduate Education Program
Medical Faculty

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FACULTY OF MEDICINE
DIPONEGORO UNIVERSITY
SEMARANG
2006

SHEET OF APPROVAL

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Faculty     : Faculty of Medicine
University: Diponegoro University
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Title          : Genetics, Hormonal, and Physical Features of Congenital Adrenal Hyperplasia Patients
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Bestari Ariningrum Setyawati 1, Sultana MH Faradz 2

Abstract

Congenital Adrenal Hyperplasia (CAH) is a familial disorder derived from reduction activity of enzymes in steroidogenesis process of the adrenal cortex that caused by a mutation of CYP21 gene located at 6p21.3. Prominent manifestation of CAH patients is ambiguity on their genitalia.

This was a descriptive observational retrospective and prospective study following genetics, hormonal, and genital features from subjects with suspected CAH. Data was obtained using medical records from the Molecular and Cyto genetic Unit in Faculty of Medicine Diponegoro University and cyto genetic laboratory of Telogorejo hospital in Semarang since April 2004 to April 2005.

Of the 79 patients diagnosed as ambiguous genitalia and hypospadia, 17 patients were suspected CAH and three of them were with mental retardation. Mutation analysis of CYP21 gene was done for 11 (64.7%) patients. Of the 8 cases (72.7%) depicted common homozygous mutations (i.e. 163 bp del, IVS2-13A>G, K102R, S493N, I172N, R356W, S268T), 6 cases (75%) demonstrated other common heterozygote mutation. Interestingly, 3 patients had heterozygous mutations (i.e. one patient with heterozygote Q318X, one with heterozygote V281L+920-921insT+Q318X and the other had heterozygote mutations I172N + R356 W all in 1 allele) manifested as simple virilizing CAH. The most frequent mutations were S493N (20%) followed by IVS2-13A>G (15%) and I172N, R356W (14%) respectively. These frequencies are rather different than other published data in Caucasian population. Among those cases were found two familial cases, patients with suspect adrenal tumours, aromatase deficiency and glucocorticoid receptor defect. Only 8 patients (47%) had specific hormonal values for CAH. Clinical stigmata were varies, however all patients developed enlarged clitoris.

Establishing physical examination alone is not effective in diagnosing CAH. Cytogenetic, hormonal assay and mutation analysis are essential for assessments.

Keywords: ambiguous genitalia, congenital adrenal hyperplasia, CAH, CYP21 gene

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Abstrak

Kongenital Adrenal Hiperplasia (HAK) merupakan kelainan familial yang disebabkan oleh menurunnya aktivitas enzim dalam proses steroidogenesis di kelenjar adrenal karena mutasi pada gen CYP21, terletak pada kromosom 6p21.3 yang mengurangi aktivitas enzim tersebut. Ambiguitas pada kelamin merupakan manifestasi utama pasien HAK.

Penelitian ini merupakan studi deskriptif observasional retrospektif dan prospektif tentang gambaran distribusi genetika, hormon dan klinis kemunculan pasien HAK. Data dianalisa dari catatan medis pada unit sitogenetik dan molekuler Fakultas Kedokteran Universitas Diponegoro dan laboratorium sitogenetik rumah sakit Telogorejo Semarang periode April 2004 sampai April 2005.

Dari 79 pasien ambigus genitalia dan hipospadia, 17 diantaranya merupakan pasien HAK dan tiga (17.65%) dari mereka merupakan pasien HAK dengan retensi mental. Sekuensing DNA pada gen CYP21 dilakukan pada 11 (64.72%) pasien. Dari 8 (72.72%) pasien yang menunjukkan mutasi homozygous (163 bp del, IVS2-13A>G, K102R, S493N, I172N, R356W, S268T), 6 pasien (75%) menunjukkan mutasi heterozygous. Menariknya, 3 pasien yang memiliki mutasi heterozygous (satu pasien dengan mutasi Q318X, satu pasien dengan mutasi V281L+920-921insT+Q318X dan pasien lain dengan mutasi I172N + R356W) menunjukkan manifestasi simple virilizing CAH. Mutasi yang paling sering ditemukan adalah mutasi S493N (20%) diikuti IVS2-13A>G (15%) dan I172N, R356W (14%) diikuti mutasi Q318X (14%). Hasil ini menunjukkan bahwa mutasi tersebut lebih sering ditemukan pada orang Kaukasia. Selain itu, ditemukan 2 kasus HAK familial, pasien dengan kecurigaan tumor kelenjar adrenal, defisiensi aromatase, dan defek pada receptor glukokortikoid. Dari 8 pasien (47.06%) didapatkan mutasi tertentu pada gen CYP21. Semua pasien menunjukkan pembesaran clitoris.

Pemeriksaan fisik saja tidak efektif untuk mendiagnosa HAK. Pemeriksaan sitogenetik, hormon, dan analisa mutasi penting sebagai pemeriksaan lanjut.

Keywords: ambiguitas kelamin, kongenital adrenal hyperplasia, HAK, gen CYP21

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Bestari Ariningrum Setyawati 1, Sultana MH Faradz 2
Kata kunci : ambiguus genitalia, congenital adrenal hyperplasia, CAH, gen CYP21
Introduction

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder caused by reduced activity of enzymes required for steroidogenesis in the adrenal cortex. This group of diseases is due to mutations in the genes encoding several enzymes needed for the production of adrenal cortex hormones. CAH comprises the most frequent cause of ambiguous genitalia in the newborn, almost 60% of all intersex cases. It produces a female pseudohermaphroditism, a genital female with virilized phenotype.1

21-Hydroxylase deficiencies become the most common cause of CAH, 90% of all CAH cases. This occurs in two forms: classical and non-classical. The classical form has two types: Salt wasting (SW), and Simple Virilizing (SV) type. The second most common cause of CAH (5-3%) of all CAH cases is the 11β-hydroxylase enzyme deficiency. Less common types of CAH are deficiencies of the following enzymes: 3-Beta-hydroxysteroid dehydrogenase; Aldosterone synthase; 17-α-hydroxylase deficiency; and mutations in the steroidogenic acute regulatory (StAR) protein.3

Clinical manifestation of CAH is different in male to that in female. Accelerated height, premature masculinization, and precocious sexual development appear in childhood are features, that commonly found in male patients. While female patients, are more jeopardized by inappropriate sex assignment, making the genitalia may appear more masculine. The clitoris is enlarged resembling a small penis. The cleft between the labia may be partly closed over (fusion of the labia majora) hiding the entrance to the vagina. Sometimes only one opening can be seen.4 In classical CAH, there is prenatal virilization of external genitalia in females graded according to severity into Prader stages I-V. There is also progressive postnatal virilization in both sexes including accelerated growth and advancement of bone age during the first years of life lead to early epiphyseal closure. Non-classic, milder forms of CAH, includes precocious puberty in children and acen, hirsutism, and menstrual irregularities in women.5 Problems that follow patients with CAH are involving medical aspects as well as psychosexual aspects. Salt wasting nephropathy occurs in 75% of infants born with CAH. Several types of tumours (adrenal, testicular, and pituitary) tend to develop in some CAH patients. If it goes unrecognized, hypertension may happen and cause collapse. Some patients can be admitted to hospital for developing cerebral atrophy, anoxic cerebral palsy and seizures. McGuire and Omenn in 1975 found indication that CAH patients do not have higher IQs than expected from family background. This is also similar to what Weneul et al, 1978 discovered. There is even a case report about CAH patients with severe mental retardation. However, the correlation between mental retardation in CAH patients is still not well understood.5,17

Clinical manifestation, hormone, and analysis of mutations on related genes encoding enzyme of steroidogenesis process are decisive for diagnosing CAH patients. In clinical data, we can see ambiguous genitalia as the main appearance of CAH cases primarily in female patients. Elevation of progesterone, 17-OH progesterone, and androstenedione and decrease of cortisol and aldosterone are prominent hormonal features of CAH. Definite diagnosis of CAH is established by having cytogenetics and molecular analysis. A karyotype of 46, XX must be found on patients with CAH, since most CAH patients who come to doctor are usually female. Male cases are usually asymptomatic.17

CYP21 gene, located on short arm of chromosome 6 (6p21.3) is a cytochrome P450 enzyme located in the endoplasmic reticulum and which catalyzes the conversion of 17-hydroxyprogesterone to 11-deoxycortisol and progesterone to deoxycorticosterone.6 Mutations are related with deletion and gene conversion on CYP21 gene.7 There were many well-known mutation on CYP21 related to CAH cases i.e 163 bp del, IVS2-13A>G, K102R, S493N, I172N, R356W, P30L, Q318X, R102K.

Unfortunately the CAH data in Indonesia is scanty, probably because many of the patients and medical personnel are less aware to seek medical treatment making majority of CAH cases are under diagnosed and untreated. Moreover most of the patients come from low socio-economic background that cannot afford the cost for examination and therapy. This has been worsening by the lack of facilities required for diagnosing CAH cases. There are two genetic laboratories in Semarang, Cytogenetics Laboratory in Telogorjo Hospital and the Molecular and Cytogenetics laboratory in Faculty of Medicine. Since the establishment of those laboratories in 1999, the CAH cases increase progressively. The present sexual adjustment team of Dr. Karadi hospital as referral hospital dealing with ambiguous genitalia in Central Java makes the diagnosis of CAH improved significantly.

This research aim is to know the distribution of genetics, hormonal, and physical features of CAH patients recorded in Cytogenetics laboratories in Semarang since April 2004 to April 2005.

Subjects and Methods

Subjects

Subjects for this research are all ambiguous genitalia patients suspected for CAH examined in two cytogenetics laboratories in Semarang. Target populations are all ambiguous genitalia patients diagnosed as CAH clinically, hormonally and genetically. This research was using a secondary data from medical records of CAH patients during period of April 2004 - April 2005. Data was obtained from physical examination, hormonal assay, cytogenetic and mutation analysis. Some of hormonal measurement and mutation analysis could not be examined in Indonesia due to financial reason.

Methods

This was a descriptive-observational retrospective and prospective study research. This research has been conducted in two places: Cytogenetics and Molecular of Biotechnology Laboratory of Medical Faculty of Diponegoro University Semarang and Cytogenetics Laboratory of Telogorjo Hospital Semarang. The sampling collection was done in the period from April 2004 to April 2005 for ambiguous genitalia patients diagnosed as CAH clinically, hormonally, and genetically. Patients suspected for CAH, then examined for further investigation. Physical examination specifically designs for CAH was done i.e. Quigley stage, Prader stage, urethrogenital swelling, phallus length, chordae, and presence of secondary sexual signs. Gender type, pedigree and photograph on genitalia were also recorded. Heparinized and EDTA peripheral blood was drawn for chromosome and DNA studies. Cytogenetic examination was performed using chromosome G banding procedure. The next step was to extract DNA from leukocytes using salting out method as elsewhere.28-29 Subsequent DNA and plasma were sent to Erasmus Medical Centre for hormonal analysis and mutation analysis.

Data processing on physical measurement and result of cytogenetic analysis was analyzed with descriptive method. The result of data processing was reported in table and chart.

Results

79 patients diagnosed as ambiguous genitalia and hypoplasia since April 2004 to April 2005, with CAH cases accounted 17 out of 79 ambiguous genitalia and hypospadia cases and three (17,65%) of them were CAH patients with mental retardation. Following are their hormonal, mutation analysis and physical examinations.
Five different hormones were examined for parameters for CAH: Progesterone, 17-Hydroxyprogesterone, Testosterone, Androstenedione, and Cortisol.

Hormonal analysis done in Rotterdam illustrated that 17 patients examined for progesterone hormone: 15 patients (88, 24%) showed elevation; 2 (11, 76%) were in normal values. For 17-hydroxyprogesterone: 14 patients (82,35%) showed elevation; 3 patients were in normal values (17,64%). 15 patients (88, 24%) showed elevation, with 2 of them (11, 76%) showed decrease for both testosterone and androstenedione hormone. For cortisol hormone: 1(5, 88%) showed elevation; 5 (29, 41%) were in normal values; 11 (64, 71%) showed decrease.

Increasing progesterone, 17-hydroxyprogesterone, testosterone, androstenedione and decreasing cortisol were found in 8 patients (47, 06%) from 17 suspected CAH. Aldosterone was not measured in this research.

Of 17 suspected CAH patients, 11 (64,70%) patients were analysed for CYP21 gene mutation. Common homozygous mutations (i.e. 163 bp del, IVS2-13A>G, K102R, S493N, I172N, R356W, S268T) were found in 8 (72,72%) cases. Six (75%) of whom also demonstrated other heterozygote mutation (i.e. compound heterozygote for I172N+S493N / I172N; P30L+R356W / R356W; I172N+R356W+S493N / S493N; S493N, I172N, R356W, S268T) were found in 8 (72,72%) cases. Six (75%) of whom also demonstrated other heterozygote mutation (i.e. compound heterozygote for I172N+S493N / I172N; P30L+R356W / R356W; I172N+R356W+S493N / S493N; S493N, I172N, R356W, S268T) were found in 8 (72,72%) cases.

Distribution of hormonal values of 17 patients diagnosed as CAH can be seen below.

Fig.1. Distribution of each hormonal measured.

Note:
Prog : Progesterone          ADIN : Androstenedione
OP-17 P: 17-Hydroxyprogesterone          COR : Cortisol
TSN : Testosterone

This study revealed variations of clinical features from CAH patients primarily on their genitalia. Most of them had stage III for Quigley (35, 29%) and stage II for Prader (23, 53%). 64,71% of patients had labia majora and minora, 29,41% had scrotum bifidum. All of patients (100%) demonstrated enlarged clitoris more than 2 cm in length, particular sign for CAH. Below are results for physical examination.

Table 2. Results of physical examination in 17 CAH patients from April 2004- April 2005.

<table>
<thead>
<tr>
<th>Clinical Examination</th>
<th>Classification</th>
<th>Total Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>10</td>
<td>58,82%</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>6</td>
<td>51,18%</td>
</tr>
<tr>
<td>Surgery Stage</td>
<td>I</td>
<td>2</td>
<td>11,76%</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3</td>
<td>17,65%</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2</td>
<td>11,76%</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>3</td>
<td>17,65%</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>5</td>
<td>29,41%</td>
</tr>
<tr>
<td></td>
<td>VI</td>
<td>5</td>
<td>29,41%</td>
</tr>
<tr>
<td></td>
<td>VII</td>
<td>4</td>
<td>23,53%</td>
</tr>
<tr>
<td></td>
<td>VIII</td>
<td>3</td>
<td>17,65%</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>2</td>
<td>11,76%</td>
</tr>
<tr>
<td></td>
<td>NE (Not Examined)</td>
<td>6</td>
<td>35,29%</td>
</tr>
<tr>
<td>Labia Majora and Minora</td>
<td>فهي 벽</td>
<td>11</td>
<td>64,71%</td>
</tr>
<tr>
<td></td>
<td>Fused Labia Majora</td>
<td>1</td>
<td>5,88%</td>
</tr>
<tr>
<td></td>
<td>Scrotum Biliform with fusion labia majora</td>
<td>1</td>
<td>5,88%</td>
</tr>
<tr>
<td>Labio Fusion</td>
<td>Fused labia majora</td>
<td>4</td>
<td>23,53%</td>
</tr>
<tr>
<td></td>
<td>Fused labia minora</td>
<td>4</td>
<td>23,53%</td>
</tr>
<tr>
<td></td>
<td>Has no fusion</td>
<td>3</td>
<td>17,65%</td>
</tr>
<tr>
<td>Clitoris</td>
<td>Enlarge (&gt; 2 cm)</td>
<td>11</td>
<td>64,71%</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>6</td>
<td>35,29%</td>
</tr>
</tbody>
</table>
Chordae Negative  (-) 16 94,12%  Positive   (+) 1 5,88%  Ending in perineal Two endings with introitus vaginae One ending  2 17,65%  Secundum secundum at very rare case  3 17,65%  Metac/publication  2 17,65%  

Discussion

Only 8 patients with specific hormonal values for CAH while the rest of the patients showed variation in hormonal values, they might have increasing testosterone and androstenedione but they had normal level of progesterone and 17-hydroxyprogesterone and vice versa. Some patients (e.g. patient no 4 and 7) received Prednisol or Desamethasone therapy nevertheless showing different cortisol level.

Genetically, CAH patients express 46. XX karyotyping for female patients or 46, XY for male patients. In this research 16 out of 17 patients (94, 11%) suspected CAH showed karyotyping of 46, XX, which is appropriate to their known gender, female. But there was 1 patient (5, 35%) whose known gender is male with 46, XX karyotyping.

There have been few reports regarding CYP21 gene mutations in Asian people. A study of 28 Singaporean revealed that the intron 2 mutation (IVS2-1A-G) was the most common mutation followed by IVS2-1B-R and R356W. This result is consistent to what Usui et al, 2004 reported from 36 Japanese patients with CAH. In contrast to the Caucasians, it was reported that the most common mutations in descending orders for British population are: large scale deletions/conversions, the intron 2 splice mutation, R357W and 1172N. Netherlands as many other western European countries has the same pattern of CYP21 gene mutation. The patterns showed the most common mutations are deletion/conversion followed by 12G, 1172N, and R356W. It was speculated that R356W mutation seems to occur more commonly in the Asian patients and less in Caucasian. In surprisingly, in this misence mutation S493N became the most frequent mutation followed by IVS2-1A-G, 1172N and R356W makes it slight different to the other published data. All of them result from gene conversion.

The salt wasting or simple virilising forms of CAH result from IVS2-1A-G mutation, is reported to be the most prevalent mutation in the CYP21 gene among all ethnic groups. In 1988, Higashi et al identified this mutation results from aberrant splicing of 1(2)conversion involving the nucleotide no 656 A-C-G. According to Miller et al, 1996 this mutation is located in intron 2, 13 bases from the splice acceptor site of exon 3. Either a C-to-G or A-to-G mutation at nucleotide 153 causes severe forms of 21-OH deficiency. While et al, 1994 mentioned that this mutation correspond to 25% of salt wasting cases, 25% of simple virilizing form, 12% of non classical cases.

The simple virilising form of CAH is often related to 1172N mutation where there was a substitution at codon 172 that results in substitution of isoleucine into Asparagine. It is a misence mutation (conversion) of CYP21 gene that only affected the structure, not the expression of the protein (Chiu et al, 1990) results in a defective enzyme (Amer et al, 1988). 1172N mutation is related to wild type of 17-hydroxyprogesterone and Progesterone activity. 8 According to Speiser et al, 1992 of 88 families with 21-OH deficiency 16% had this mutation, with 2% enzyme activity and a simple virilizing phenotype.

The R356W mutation is associated with the non-classical type of 21-OH deficiency, where Arginine (Arg) 356 is replaced by Tryptophan. It is a missence mutation (conversion) results in radicular Amino acid substitution (Chiu et al, 1990).

In this research there was also found one heterozygous patient for mutation P30L, a substitution of Leucine to Proline at codon 30. P30L is also somewhat related to wild activity of 17-hydroxyprogesterone and Progesterone as much as 60% and about 30% of normal activity for Progesterone. This type of mutation is presumed to be potentially giving effects to the non-classical type of 21-OH deficiency (Tanie et al, 1991).

Glutenase is changed to stop codon in Q318X mutation. This may result in a completely non-functional enzyme due to premature termination of translation of the mRNA. A homogency mutation for this gene results in salt wasting type of CAH, while compound heterozygous mutation in this gene is associated with simple virilizing form (Kharut et al, 2004). Dacopoulos-Vahabli et al, 2001 found that P30L mutation is happened in 21.4% in the non-classical form from 111 unrelated subjects in the Hellenic population.

163 bp del is best described as 3 base pairs deletion/insertion (Ls deletion/insertion) downstream codon 9. As described in many literature insertions 3 base pairs GTG has no effect on the enzymatic activity, and it is assumed that such change is a non-functional mutation (Rodrigues et al, 1987).

Speiser et al, 1988 detected a change in codon 281 from GTG, encoding Valine, to TTG, encoding Leucine in 9 non-classical 21-OH deficiency patients. White et al, 1994 mentioned that 34% of all non-classical type is due to this mutation.

White Morritt et al, 1991 mentioned that the val-281-to-leu mutation accounts for 75 to 80% of non-classical 21-hydroxylase deficiency. Other mutations found were K102R, S493N and S268T. Both K102R and S493N are non-functional mutations (Rodrigues et al, 1987). While it can be inferred that S268T mutation is non-functional mutation, which does not cause CAH (Tasie-Lunus et al, 1991).

Patient no 1, 13 year old girl was with virilization on her genitalia. Established hormonal measurement indicated normal level of progesterone, and 17-hydroxyprogesterone despite the increasing of testosterone, androstenedione and decreasing of cortisol. There was no confirmation on CYP21 gene related to 1172N mutation, which can be understood since she had normal 17-hydroxyprogesterone, signifying no presence of mutation. However there was an increasing testosterone, led to masculinization for her.

It was speculated that R356W mutation seems to occur more commonly in the Asian patients and less in Caucasian. Other factors should be considered as part of the explanation since in most genetic cases environmental factors play a tribute role for the phenotype of patients. Therefore further investigation should be done to confirm this phenomenon.

Patient no 13, a month year old baby girl come with virilization on her genitalia. Established hormonal measurement indicated normal level of progesterone, and 17-hydroxyprogesterone despite the increasing of testosterone, androstenedione and decreasing of cortisol. There was no confirmation on CYP21 gene mutation. It is possible that she is suffered from glucocorticoid receptor defect.

Patient no 14, an 8-year-old girl with ambiguous genitalia, showing phenotype of CAH (diabetes enlarged- see fig. 3) but levels of 17-hydroxyprogesterone and androstenedione are relatively normal. This excludes a CYP21 block. But the cortisol level is relatively low. Testosterone is below detection level, despite this girl had no steroid therapy. These indicate to a block early in steroid biosynthesis, probably at the level of cholesterol side chain cleavage or the STAR protein. The other consideration on explaining this feature is that this girl might suffer from aromasate deficiency. However another molecular analysis for this patient and her father also done in Nijmegen, and the result is that she and her father shared same type of heterozygous mutation V281L = +920-921insT+Q318X. Her mutation is located at the exact same allele as her father. Molecularly she and her father are confirmed to be carrier CAH, but this does not explain such phenotype on the genitalia she demonstrated. Therefore it is possible that other mutations are present on the other areas of the gene.

Two familial CAH cases were also found. Patient no 3 (see fig 4) and no 9 were sisters with simple virilized of CAH. Both demonstrated the same compound heterozygous mutation of 1172N= S493N/ S268T. They were also having elevation of 17-hydroxyprogesterone, testosterone and androstenedione although patient no 3 was having relatively normal level of cortisol while her sister had low level of cortisol. The other familial CAH cases were patient no 2 and no 11. Patient no 2 seemed to show a more severe form of virilization. It is quite understandable since she (patient no 2) demonstrated more frequency of homozygote mutation compared to her sister. As the other CAH family case, these patients also had same pattern of elevation of 17-hydroxyprogesterone, testosterone and androstenedione despite no 2 was having relatively normal level of cortisol while her sister had low level of cortisol.

The exposure of androgens in both classical CAH and nonclassical 21-hydroxylase deficiencies may cause accelerated linear growth velocity and diminished final height in both males and females. This is similar to 3 of our cases (patient no2, 4 and 6) that displayed an adult short stature. Patient no 2, 17 year old girl with severe virilization CAH was having final height 145.5 cm. Patient no 4 is 21 year old girl with simple virilization CAH was having final height of 150 cm. While patient no 6 is 33 year old girl who manifested simple virilization CAH with final height of 149.5 cm.
Many variations were found in the physical examination of patients, therefore physical features could not be used alone in establishing the diagnosis. Other examination such as hormonal assay and mutation analysis of CYP21 gene is needed. Conversely most patients were from low socio-economic level that they could not afford the cost of laboratory examination and therapy as well.

A cytogenetics laboratory is necessary to perform the genotype of ambiguous genitalia patients, but this laboratory only available in 4 cities in Java island for whole archipelago with the population about 220 million. Patients from rural areas who may have ambiguous genitalia can be barely detected. It results in the diagnosis of CAH is neither yet well-established nor well detected and lead to incorrect treatment.

Issues about ambiguous genitalia and CAH in Indonesia up to now are less popular around medical personnel and even in the community. There was an increasing tendency of ambiguous genitalia patients seek for medical treatment during the progress of this research. Unfortunately, most of them came late, this made the further management and therapies more complicated. The delay of CAH patients admitted to hospital causes some of them develop more complex abnormalities such as seizures, cerebral atrophy, cerebral palsy, or mental retardation.

Thus, it is suggested to conduct other research to provide a better understanding about CAH, prevalence of CAH in Indonesia and give new insight into the underlying process.

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List of Abreviations

1. CAH : Congenital Adrenal Hyperplasia
2. STAR : Steroid Acute Regulatory Protein
3. bp : base pairs
4. del : deletions
5. IVS2 : interfering sequence 2
6. ins : insertion
7. A : nucleic acid code for adenine
8. G : nucleic acid code for guanine
9. I : amino acid code for isoleucine
10. K : amino acid code for lysine
11. L : amino acid code for leucine
12. N : amino acid code for asparagine
13. P : amino acid code for proline
14. Q : amino acid code for glutamine
15. R : amino acid code for arginine
16. S : amino acid code for serine
17. T : amino acid code for threonine
18. V : amino acid code for valine
19. W : amino acid code for tryptophan
20. X : stop codon (TAG or TAA)