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The Role of Multimodalities Approach in Diagnosing Disorders of Sex Development (DSD): Brief Review

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Abstract

Disorders of Sex Development (DSD) encompass rare congenital conditions involving atypical development of chromosomes, gonads, or sex anatomy. The 2006 global consensus led to a shift in the approach to handling DSD cases, emphasizing integrated treatment involving various scientific disciplines. DSD diagnosis involves a structured and multimodality approach, including history, pedigree analysis, physical examination, imaging, hormone and chromosome analysis, and genetic testing. An in-depth anamnesis and detailed pedigree analysis help trace family history and inheritance patterns of Mendelian traits in DSD cases. Thorough physical examination, including general and specific assessments, helps screen for abnormalities in sexual development. Karyotyping, hormone level investigation, and imaging examinations are crucial for supporting the diagnosis of DSD. However, genetic or molecular examination remains the modality for definitively confirming the genetic disorder underlying DSD, subsequently leading to a better understanding and management of the condition. Considering the limited resources available in the field in efforts to establish a molecular diagnosis of DSD, it is recommended to explore the role of anamnesis, pedigree analysis, physical examination, imaging examination, hormonal laboratory examination, and chromosome analysis in efforts to approach the diagnosis of DSD.

Keywords: Disorders of Sex Development, DSD, Diagnosis

1. Introduction

Disorders of Sex Development (DSD) is a collective term for a group of rare congenital disorders characterized by atypical development of chromosomes, gonads, or sex anatomy.[1,2,3] The use of the term DSD was agreed upon in 2006 through a global consensus issued by the Pediatric Endocrine Society and the European Society of Pediatric Endocrinology.[1]

Apart from changes in the use of terms, this consensus also brought about a change in the approach to handling DSD cases to an integrated treatment involving various scientific disciplines.[1] This change in approach to handling DSD cases is in line with the complexity of the DSD condition with all its clinical variability. The clinical variability of DSD itself includes various physical examination findings of the external genitalia, internal reproductive organs, variations in levels of hormones, and chromosome analysis, which poses challenges in establishing a diagnosis of DSD.[2,4,5] This review will briefly provide insight into how the multimodality approach may aid in establishing the DSD diagnosis.

2. The Structured Approach in Diagnosing DSD

In general, DSD can be broadly categorized into (1) 46, XX DSD, (2) 46, XX DSD, and (3) Sex Chromosome DSD.[1,2] However, considering the complexity of DSD, the diagnosis also requires a structured and multimodality approach, carried out in stages.[1,4] Several recommended stages of the DSD diagnostic approach include: (1) History, (2) pedigree analysis, (3) physical examination, (4) imaging examination, (5) hormone laboratory examination, (6) chromosome analysis, and (7) genetic or molecular examination as the gold standard examination for diagnosing DSD.[1,4-6]

In a series of structured DSD diagnosis processes, the initial stages of this process are anamnesis and physical examination. An in-depth and detailed anamnesis including tracing the family tree (pedigree) and a history of consanguinity is an initial action that must be carried out in managing DSD cases.[6-8] Preparation of a pedigree or family tree supported by tracing the history of consanguinity can help provide clues regarding the pattern of inheritance of Mendelian traits found in the DSD cases faced.[6-10]

Armed with the findings from the initial stage of history taking and preparation of a three-generation pedigree, the next modality in establishing a diagnosis of DSD is a thorough physical examination. This physical examination includes a general and specific physical examination of related organs.[6,10] A general physical examination is carried out as is usually done on other patients, such as anthropometric measurements and examination of vital signs, to assess the patient's general condition first.[6, 10] The specific examination carried out later will focus more on dysmorphology and other clinical findings related to DSD.[10] The results of these two initial examination stages can help screen for the presence or absence of abnormalities in sexual development, which are then followed up with supporting examinations in the form of hormone laboratory tests, ultrasound imaging, chromosome analysis, and genetic/molecular examination as the gold standard examination.[4,6,10]

Of the various examination modalities to support the diagnosis of DSD, karyotyping or chromosome analysis is an initial examination that can be carried out to determine the general classification of DSD based on the Chicago consensus in 2006.[1,2,11] Furthermore, to narrow down possible diagnoses, hormone levels evaluation, and imaging examinations are also important to do. Investigation of hormone levels as part of the DSD diagnosis process provides valuable information regarding the function of the gonads and adrenal glands in DSD cases. Examining these hormone levels can also help identify various possible pathogenesis mechanisms underlying DSD.[12] One of the most informative parameters is the level of the hormone 17-hydroxyprogesterone (17-OHP) at 46, XX DSD, and the level of luteinizing hormone at 46, XY DSD.[12,13]

Apart from physical examination of the external genital organs, examination of the internal reproductive organs is also mandatory because the clinical variability of DSD also includes variations in the internal reproductive organs. An imaging examination can be taken to evaluate the structure of the internal reproductive organs.[14,15] One of the main and first modalities that are easy and cheap to carry out in assessing the structure of the internal reproductive organs in DSD cases is an ultrasound examination.[15]

Of all the modalities for establishing a diagnosis of DSD, genetic or molecular examination is the main modality for establishing a definite diagnosis that can confirm with certainty the genetic disorder

that causes DSD. [5] By knowing the molecular etiology or genetic variations that underlie a DSD, then The natural course of a DSD condition can be better understood.[5] This better understanding and knowledge can help health workers in the management of DSD patients, which in turn can help improve the quality of life and patient outcomes, both short and long-term.[3] Unfortunately, although genetic testing is the backbone of the approach to definitive diagnosis of DSD, it is not yet widely available to the global community. Countries with inadequate resources often experience obstacles in establishing a definite diagnosis of DSD through genetic examination, including Indonesia.[16-18]

3. Conclusion

Given the constraints of resources in the field, when aiming to establish a molecular diagnosis of DSD, it is advised to investigate the significance of patient history, familial history assessment, physical examination, imaging studies, hormonal laboratory tests, and chromosome analysis as part of the diagnostic process.

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