



Case Report

Cornelia de lange syndrome with thyroid agenesis of an Indonesian patient

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Abstract: Cornelia de Lange syndrome (CdLS), which is also called Brachmann de Lange syndrome, is a congenital disorder characterized by distinctive facial features, prenatal and postnatal growth deficiency, feeding difficulties, psychomotor delay, behavioral problems, and associated malformations that mainly involve the upper extremities. The prevalence ranges from 1:100,000 to as high as 1:10,000. Most cases (50-60%) were carried mutation in NIPBL gene. To our knowledge this is the first CdLS Indonesian case that reported with molecular analysis study. We present an 11 months old female Indonesian patient with classic CdLS with congenital hypothyroid. Genetics studies were performed in intron 1, exon 2, exon 10 and exon 22 of NIPBL gene. Thyroid studies (T3, T4, TSH and thyroid scan) were performed. Low level of T3 and T4, and high level of TSH were observed. Thyroid agenesis was found in thyroid scan examination. We detected thyroid agenesis which has been never reported in CdLS patients. We could not find any mutation in intron 1, exon 2, exon 10 and exon 22 of NIPBL gene. Further genetics examinations were necessary whether there is mutation in other locus.

Key words: CDLS; Mutation analysis; Thyroid agenesis.

Introduction

Cornelia de lange syndrome (CdLS) is a congenital disorder indicated by craniofacial defects, prenatal and postnatal growth retardation, feeding difficulties, psychomotor delay, and behavioral problems (1). The abnormalities include facial dysmorphism (arched eyebrows, synophrys, depressed nasal bridge, long philtrum, and down turned angles of the mouth), upper-extremity malformations, hirsutism, cardiac defects, and gastrointestinal alterations (2, 3). Clinical finding should meet facial criteria, and two to three of six other system categories (4). The prevalence of CdLS is difficult to estimate as individuals with milder features are likely under-recognized. The prevalence range from 1:100,000 (5), to as high as 1:10,000.(6) Recent data from the EUROCAT dataset have estimated the prevalence at 1:50,000 for the classic form of CdLS (7). Most cases (50-60%) were carried mutation in NIPBL gene (8).

Case Report

An 11 month-old girl was presented to Hasan Sadikin Hospital with complaints of shortness of breath and vomiting. Patient was already being treated for the seventh time since the first time she had similar complaints. Patient was a low birth weight baby (1700 grams), with unknown birth body length. Patient has been treated in local hospital three times with only two days interval between visits. Patient then was referred to Hasan Sadikin Hospital, hospitalized for one month, and during hospitalization she was diagnosed with as-

piration pneumonia, congenital hypothyroidism and severe bilateral hearing disorder. On physical examination we found severely underweight, severely stunted, failure to thrive, dysmorphic face, long eyelashes, synophrys, short nose, anteverted nostrils, depressed nasal bridge, small chin, micrognathia, and clindactily. Complete blood counts and urine examinations were within normal limits; intracardiac echocardiography showed normal result; and there was a decrease in hypothyroid hormone T3, FT4 and increased TSHs, while the result of thyroid scan was thyroid agenesis. Patient is currently undergoing chromosomal and cortisol examination. She has having eutyax therapy and was fed by nasogastric tube.

Discussion

Congenital de lange syndrome is a complex congenital malformation with a number of systemic abnormalities and impairment on the quality of life of affected subjects and their families. The diagnosis is based on clinical sign and symptoms of a distinct phenotype, mainly in the face and limbs. The associated sign and symptoms of this disorder vary widely among affected individuals. Referring to Van Allen et al, the characteristic of type I or classic CdLS patients include facial and skeletal changes. They have prenatal growth deficiency, psychomotor delay, and major malformations, that leads to severe disability or death. In type II or mild CdLS patients, similar facial and minor skeletal defects are also found. However, these develop with time or are



Figure 1. Appearance of case.

partially expressed. They have mild to borderline psychomotor delay, less severe pre- and postnatal growth deficiency, and the absence of (or less severe) major malformations. Type III or phenocopy CdLS have phenotypic manifestations of CdLS associated to chromosomal aneuploidies or teratogenic exposures (9). In this case the patient was found to have thyroid agenesis. To our knowledge, CDLS patients with congenital hypothyroid due to thyroid agenesis has never been documented in the literatures.

NIPBL is the gene most predominantly found to be mutated in subjects with CdLS that causes both mild and severe forms (8-10). Previous study reported that, in 53% of the mutations analyzed, 55% demonstrated a detectable mutation in NIPBL or SMC1A, and individuals with missense mutations in NIPBL and SMC1A presented with milder symptoms than exhibited with other mutations (4). In other study on NIPBL gene, it has been identified 25 missense mutations, 19 nonsense mutations, 13 splicing mutations, 26 deletions mutations, and 16 insertion mutations (11).

In this study, there was no mutation detected in intron 1, exon 2, exon 10 and exon 22 NIPBL gene. Previously, two groups have reported a low frequency of large genomic rearrangements in CDLS. Ratajska *et al.* (12). studied 11 NIPBL/SMC1A mutation-negative cases and found one deletion spanning 62.7 kb and encompassing exons 35–47 of the NIPBL gene. Bhuiyan *et al.* (13). analyzed 50 CDLS probands negative for NIPBL mutation and found a single 5.2-kb deletion encompassing exons 41–42 of NIPBL.

In conclusion, we report an Indonesian CDLS patient with a thyroid agenesis as a rare condition. Unfortunately, we could not detect mutation in intron 1, exon 2, exon 10 and exon 22. Further genetic testing is necessary to detect mutation in other locus. Detail investigation should be done whether thyroid agenesis is a distinct phenotype from CDLS or might be related to the disease.

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Conflict of interest

Authors declare that there is no conflict interest.

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