CASE REPORT

Cornelia De Lange Syndrome in the International Classification of Functioning, Disability and Health Perspetive: A Case Report

Albert Setiawan[1], Nunung Nugroho[1,2], Thirza Hadipranata[3], Bernadheta Ayu Andriani[3], Jennifer Anggraini Sasangka[4]

[1] Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Widya Mandala Catholic University, Surabaya, Indonesia

[2] Department of Physical Medicine and Rehabilitation, Primasatya Husada Citra Hospital, Surabaya, Indonesia

[3] Alumni of the Faculty of Medicine, Widya Mandala Catholic University Surabaya, Indonesia

[4] Clinical Clerkship Program, Faculty of Medicine, Widya Mandala Catholic University Surabaya, Indonesia

ABSTRACT

Background: Cornelia de Lange syndrome (CdLS) is a genetic disorder featured by multi-systemic malformations, such as microcephaly, hypertrichosis, upper limb defects, growth retardation, developmental delay, and other associated malformations. Multidisciplinary and holistic care is needed to manage and rehabilitate individuals with CdLS. One of the tools that can be used as a clinical measurement in holistic care is the International Classification of Functioning, Disability, and Health (ICF).

Objective: To provide a holistic approach and intervention using the ICF assessment in CdLS individuals.

Case: A 53-month-old boy was admitted to the Physical Medicine and Rehabilitation outpatient clinic of Primasatya Husada Citra (PHC) hospital of Surabaya in February 2021 due to global developmental and growth delay. The patient had low body weight and short stature. The patient had thick eyebrows, a short nose, a concave nasal ridge, thin upper lip vermillion, smooth philtrum, and small hands with small fifth fingers. He was only able to say several words unclearly pronounced. During daily activities, he had difficulty going upstairs and downstairs and wearing his socks, long pants, and a shirt. He attended preschool and had difficulties with speaking, reading, and focusing attention.

Conclusion: ICF can help physicians assess a patient's condition comprehensively, set goals, and provide appropriate treatment and rehabilitation programs for CdLS patients.

Keywords: Cornelia de Lange Syndrome, International Classification of Functioning Disability and Health, Rehabilitation, Pediatrics

ABSTRAK

Latar belakang: Cornelia de Lange Syndrome (CdLS) adalah kelainan genetik yang ditandai dengan malformasi multi-sistemik. Perawatan multidisiplin dan holistik diperlukan dalam pengelolaan dan rehabilitasi individu dengan CdLS. Salah satu alat yang dapat digunakan sebagai ukuran klinis dalam perawatan holistik adalah International Classification of Functioning, Disability, and Health (ICF).

Tujuan: Untuk melakukan pendekatan dan intervensi holistik dengan menggunakan penilaian ICF pada individu CdLS.

Kasus: Seorang anak laki-laki berusia 53 bulan datang di klinik Kedokteran Fisik dan Rehabilitasi di RS Primasatya Husada Citra (PHC) Surabaya pada Februari 2021, karena keterlambatan perkembangan dan pertumbuhan secara global. Pasien memiliki berat badan rendah dan perawakan pendek. Pasien memiliki alis tebal, hidung pendek, tonjolan hidung cekung, vermillion bibir atas tipis, filtrum halus, dan tangan kecil disertai dengan jari kelima kecil. Hanya bisa mengucapkan beberapa kata dan pengucapannya tidak jelas. Selama aktivitas sehari-hari, ia kesulitan dalam naik dan turun anak tangga, memakai kaus kaki, celana panjang, dan kemeja. Ia saat ini menghadiri pra-sekolah, tapi mengalami kesulitan berbicara, membaca, dan memusatkan perhatian.

Kesimpulan: ICF berguna untuk menilai kondisi pasien, menetapkan target terapi, dan program rehabilitasi yang tepat untuk penderita CdLS.

Kata kunci: Cornelia de Lange Syndrome, International Classification of Functioning Disability and Health, Rehabilitasi, Pediatri

Correspondent Detail:

Albert Setiawan

Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Widya Mandala Catholic University.
Jl. Raya Kalisari Selatan no. 1, Surabaya.
Fax: +6231-99005277.
Email: albert_setiawan@ukwms.ac.id.
Phone number: +62811377174.

INTRODUCTION

Cornelia de Lange syndrome (CdLS) is developmental multiple congenital anomalies with cognitive and behavioral characteristics. It was initially reported by Brachmann (1916) and further characterized by de Lange (1933).[1] The prevalence of this syndrome is between 1:30,000 and 1:10,000.[2] To date, there is no description of differences based on gender or race.[3]

CdLS is caused by pathogenic variants in any one of seven genes (NIPBL, SMC1A, SMC3, RAD21, BRD4, HDCA8, and ANKRD11) that play a role in cohesion complex, namely cohesinopathies. The NIPBL gene is present in approximately 70% of individuals.[4]

It is classified into two groups, classic and non-classic CdLS. The classification is based on the consensus criteria scores: cardinal features and suggestive features of CdLS. The patient is considered a classic CdLS if the patient scores 11 points or more, with at least three cardinal signs. Patient is considered non-classic CdLS if the patient scores 9 or 10 points with at least two cardinal signs. Meanwhile, patients with a lower score will need further molecular testing to confirm CdLS.2 Patients with CdLS may have several organ system manifestations and problems, including gastroenterology, ophthalmology, ear, nose and throat, musculoskeletal, neurology, cognition, and behavior.[2] Due to various manifestations, a multidisciplinary diagnostic approach and comprehensive treatments are required to optimize the patient's growth and developmental stage, prevent potential complications, and improve the patient's well-being and life expectancy.[2]

The International Classification of Functioning, Disability, and Health (ICF) was established by WHO in 2001 to describe a person's health.[5] The ICF assessment includes two parts, functioning and disability (Body functions and structures, activity, and participation) and contextual factors (environmental and personal factors). ICF components will affect each other's overall individual function.[5] In its development, WHO established a specific ICF for children and adolescents named ICF-Children and Youth (CY). The ICF-CY has the same classification structure as the adult, with several additional and modified items to meet the need for the children and youth assessment.[6] Using ICF is beneficial in handling a case especially to provide standard language and framework for describing health and health-related conditions, a scientific basis for understanding and studying the patient comprehensively, to establish international and multidisciplinary interventions and handling, and to be an internationally accepted systematic coding scheme.[5] In a study, ICF was used to assess the success of Intensive Neuromotor Therapy (INMT) on participation and gross motor function in children with CdLS.[7]

Early diagnosis and intervention in CdLS patients are important to handle the problems, prevent disabilities, and improve the patient's future quality of life. CdLS is a challenging case, especially for the Physical Medicine and Rehabilitation (PM&R) Department, due to various disabilities that may occur to the patient. The authors would like to focus on the clinical diagnostic approach using the ICF assessment.

CASE DESCRIPTION

A 53-month-old boy was admitted to Physical Medicine and Rehabilitation clinic at Primasatya Husada Citra (PHC) hospital of Surabaya in February 2021 due to global developmental and growth delay. The patient had low body weight and short stature.

From maternity history, there were no pathological symptoms, consuming drugs, or any diseases during the pregnancy. The patient is the first child, spontaneous birth at the maternity age of 35/36 weeks with a birth weight of 2400 grams, and he was crying spontaneously and had no cyanosis. Before labor, the amniotic sac broke, and the amniotic fluid was cloudy. Due to the low birth weight, the patient was treated in a simple incubator for a day. There was a history of stagnant and

even declining body weight. As time passed, the patient began to grow and develop, but the parent noticed lateness compared to the other children. The patient was fully vaccinated with the basic immunization requirement.

From the physical examination, his body weight was 8.5 kg (weight for age 5th percentile), body height was 81 cm (height for age 5th percentile), with a body mass index, height to weight (BMI) of 12.96 kg/m^2, head circumference of 39.5 cm (head circumference for age 2nd percentile), with normal vital signs. There was no vision or hearing problem. Through inspection, the patient had thick eyebrows, a short nose, a concave nasal ridge, thin upper lip vermillion, smooth philtrum (Figure 1), and small hands with small fifth fingers (Figure 2).

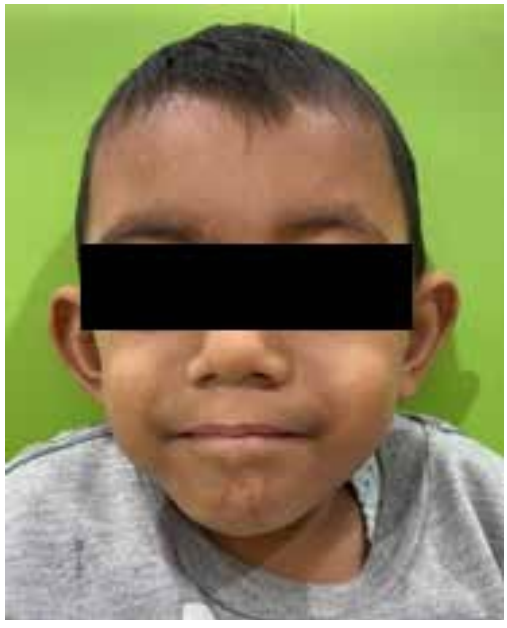

Figure 1. Face appearance showing thick eyebrows, short nose, concave nasal ridge, thin upper lip vermillion & smooth philtrum.

Figure 2. Small hands with small fifth fingers.

The patient could say several words unclearly pronounced. During the daily activities, he had difficulty going downstairs and wearing socks, long pants, and a shirt. He attended preschool and had difficulties with speaking, reading, and focusing attention. However, he had no limitations during physical activity and was able to play with his friends.

Further diagnostic tests of laboratory and radiology were done. The laboratory test of FT4 and TSH, both showed normal results. According to the information obtained through anamnesis, physical examination, and laboratory tests, the patient was diagnosed with Cornelia de Lange syndrome (CdLS). According to the consensus scoring system, the patient scored 12 points (Table 1). Because this is a rare finding of CdLS patient, we asked the patient's parents regarding informed consent for this case report. From the diagnosis and finding, we arranged an ICF model (Figure 3).

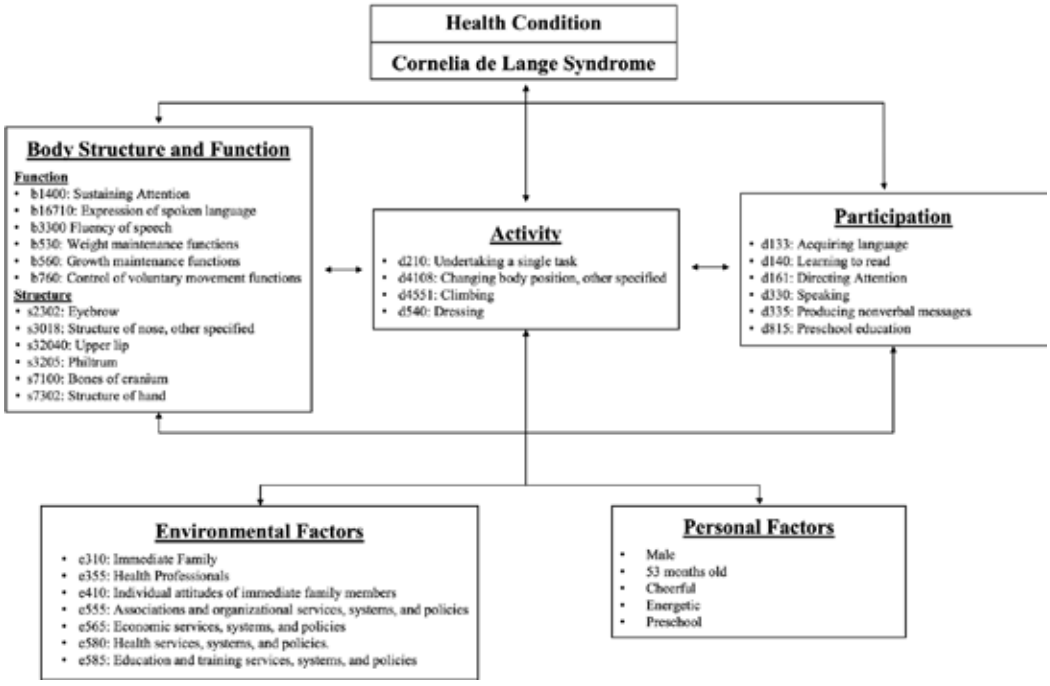

Figure 3. International Classification of Functioning, Disability and Health (ICF) Diagram of The Patient.

Table 1. Table of Cornelia de Lange Syndrome Clinical Features & Scoring

Clinical Features of CdLS	Patient's	Points
Cardinal Features (2 points each)		
Synophyrs and/or thick eyebrows	Yes (Thick eyebrows)	2 points
Short nose, concave nasal ridge, and/or upturned nasal tip	Yes (Short nose, concave nasal ridge)	2 points
Long and/or smooth philtrum	Yes (Smooth philtrum)	2 points
Thin upper lip vermillion and/or downturned corners of the mouth	Yes (Thin upper lip vermillion)	2 points
Hand oligodactyly and/or adactyly	Not found	0 point
Congenital diaphragmatic hernia	Not found	0 point
Suggestive features (1 point each)		
Global developmental delay and/or intellectual disability	Yes	1 point
Prenatal growth retardation (< 2SD)	No data	0 point
Postnatal growth retardation (< 2SD)	Yes	1 point
Microcephaly (prenatally and/or postnatally)	Yes	1 point
Small hands and/or feet	Yes (Small hands)	0 point
Short fifth finger	Yes	1 point
Hirsutism	Not found	0 point
Total 12 points		

The treatment for CdLS patients is interdisciplinary and individualized. The patient has undergone treatment with an occupational therapist to catch up with the development and focus and a speech therapist to improve his speaking skills. For occupational therapy, the patient went to Snoezelen room with task-oriented training to improve focus and attention. In speech therapy, we treat the patient with word concept, phonation and articulation, syllable and word forming, word vocabulary, and sentence forming exercises. Treatments were given to prevent further complications, catch the development, and improve the patient's quality of life. We made rehabilitation planning (Table 2) according to the problems attained from ICF diagram (Figure 3), and setting short- and long-term goals.

Table 2. Planning of Patient's Condition According to the ICF

Problems	Goal	Planning
Communication and Language • Speech delay • Dysarthria • Reading difficulty	**Short-term goals:** • Able to say clear and proper words • Reading training **Long-term goals:** • Achieve clear speech articulation • Able to talk in sentence • Able to read • Independent ADL • Improved quality of life	**PTx:** Speech Therapy: • Language concept exercise • Phonation and articulation exercise • Syllable and word forming exercise • Word vocabulary exercise • Sentence forming exercise **PEx:** • Continue exercise and stimulation at home
Social and Environmental • Attention deficit • Limited inclusive school for education in Indonesia • Lack of CdLS support group	**Short-term goals:** • Improve attention and focus • Join the CdLS support group online **Long-term goals:** • Able to get proper education • Able to get information about the patient's disease and need • Independent ADL • Improved quality of life	**PTx:** Occupational Therapy: • Attention training with task-oriented in Snoezelen room **PEx:** • Continue exercise and stimulation at home • Educate the patient's parents to enroll inclusive school in Indonesia • Educate the patient's parents to actively share information online or offline with other parents with CdLS children and to get suggestions from the other families in the community.
Motor (Gross and Fine Motor) • Inability of dressing (put on socks, pants) • Inability of going upstairs and downstairs	**Short-term goals:** • Able to ambulate normally in difference surface level & in stairs • Improve muscle strength in both legs • Dressing training **Long-term goals:** • Independent ADL • Reduce fall risk • Improved quality of life	PTx: Strengthen lower extremity muscle with playing, such as kicking ball Counterpoise exercise for climbing stairs and dressing ADL exercise (put on and take off shirt, pants, and socks according to age) PEx: Continue exercise and stimulation at home

Problems	Goal	Planning
• Underweight • Abnormal body structures (short stature, small fingers, thick eyebrows, a short nose, a concave nasal ridge, thin upper lip vermillion, smooth philtrum)	**Short term goals:** Help the patient's parents better understand the patient condition **Long term goals:** Achieve normal weight according to CdLS growth chart	**PDx:** Consult nutritionist for patient's low body weight **PEx:** • Educate the patient's parents about the patient's condition and the treatment that the patient will get • Eat nutritious food according to the nutritionist's suggestions

CASE DISCUSSION

CdLS is a rare genetic condition caused by the pathogenic variants in NIPBL, SMC1A, SMC3, RAD21, BRD4, ANKRD11, and HDAC8 genes featured by multiple congenital anomalies, mental and growth delay, and other malformations associated to CdLS.[8] The prevalence of CdLS in Europe is estimated to be 1.24 per 100.000 birth, in which female-to-male ratio is higher.[9]

As no set of clinical criteria existed for diagnosing mild cases until the recent introduction of molecular testing, there was no diagnostic certainty in diagnosing mildly affected patients.[9] In this case, a 53-month-old boy was referred by the pediatrician with global developmental delay. He had four cardinal features (thick eyebrows, short nose, concave nasal ridge, smooth philtrum, and thin upper lip vermillion), had five suggestive features (global developmental delay and intellectual disability, postnatal growth retardation, microcephaly, small hands, and short fifth finger), and scored 12 points according to the expert consensus document of CdLS.[2] Mehta et al. showed a CdLS case without hand oligodactyly and/or adactyly features.[10] In another case report, a CdLS patient was diagnosed without limb malformation criteria.[11] Cheng et al. found that CdLS patients had small hands with small 5th fingers12. However, we found no hand oligodactyly and/or adactyly from the patient. The patient had small hands compared to average children, a brachyclinodactyly of the 5th fingers, and no hirsutism.[13] Laboratory tests of FT4 and TSH were normal; it rules out congenital hypothyroidism. He was able to say several words unclearly pronounced. During the daily activities, he had difficulties going downstairs and wearing socks, long pants, and a shirt. He was attending preschool and had difficulties in speaking, reading, and focusing attention. Mikolajewska found a delay in functional abilities of eye contact, moving or carrying body weight, contractures, deformities, and standing in children with CdLS.[14] ICF perspective is used for a holistic and comprehensive approach, as shown in Figure 3. The treatment in CdLS is mainly individualized according to each patient's problems and requires an interdisciplinary team.[15] A review by Mikolajewska suggested that speech therapy can be given to CdLS

patients with speech retardation and deficits, and occupational therapy can be given to CdLS patients with motor disorders and developmental retardation.[15] Both therapies were done to catch up on the developmental delay.[13]

After a series of occupational and speech therapy, there were improvements in four developmental domains. Kline et al. found that children with CdLS benefit greatly from occupational, physical, and speech therapy in their early childhood.[13] Physical therapies should begin as early as possible for better developmental outcomes.[13] At preschool, he could focus for a longer duration and showed frequent and appropriate eye contact. He understood commands, could participate in communications with single syllable, and could put on clothes and trousers independently. Kline et al. found psychomotor development in CdLS patients has a normal development with 95% accomplished at the same age.[16]

From the last follow-up, the patient is 5-years-old with a weight of 10 kg (50th percentile, weight to age), a height of 90 cm (50th percentile, height to age), and a head circumference of 41 cm (2nd percentile, head circumference to age) according to the growth charts of children with CdLS by Kline et al.[17] Individuals with CdLS can gain weight with high-calorie formulas though they grow at their own pace because of high metabolic rate.[13]

The patient's family joined the CdLS online support group in Indonesia. Families benefit greatly from the support of other families in similar situations.[13] Griffith et al. found high level of parental stress and mental health problems in the parents of CdLS, and they often have difficulties accessing medical and social services.[18] The online support group and social media platforms are helpful for the family in sharing experiences and feelings, finding emotional support, and empowering patients with similar conditions.[19]

We educate parents to enroll him in an inclusive school, which is an educational service system in Indonesia for children with special needs. They are enabling children to have the opportunities to participate in schools with the non-disabled peers of their age.[20] According to the Regulation of the Minister of National Education Number 70 of 2009 on the Inclusive Education Article 3 Paragraph 1 states that students with physical, emotional, mental, and social disorders or have the potential for intelligence and/or special talents are entitled to participate in inclusive education in certain educational units according to their needs and abilities.[20] Enrolling the patient into inclusive school will help him meet the needs and support the learning and participation of the patient.

CONCLUSION

CdLS is a rare genetic condition due to pathogenic variants in the cohesin complex. It is characterized by unique facial features such as synophyrs, growth deficiency, mental and psychomotor delay, behavioral problems, and malformations of the upper extremities. This case report shows the importance of holistic and comprehensive care for children with CdLS to achieve a better quality of life. ICF can be used to assess a patient's condition, set goals, and provide condition-appropriate treatment and rehabilitation programs for CdLS patients.

REFERENCES

1. Masciadri M, Ficcadenti A, Milani D, Cogliati F, Divizia MT, Larizza L, et al. Recurrence and Familial Inheritance of Intronic NIPBL Pathogenic Variant Associated with Mild CdLSs. Front Neurol. 2018 Nov 27;9(NOV).
2. Kline AD, Moss JF, Selicorni A, Bisgaard AM, Deardorff MA, Gillett PM, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Vol. 19, Nature Reviews Genetics. Nature Publishing Group; 2018. p. 649–66.
3. Dowsett L, Porras AR, Kruszka P, Davis B, Hu T, Honey E, et al. Cornelia de Lange syndrome in diverse populations. Am J Med Genet A. 2019 Feb 1;179(2):150–8.
4. Liu C, Li X, Cui J, Dong R, Lv Y, Wang D, et al. Analysis of clinical and genetic characteristics in 10 Chinese individuals with Cornelia de Lange syndrome and literature review. Mol Genet Genomic Med. 2020 Oct 1;8(10).
5. World Health Organization. International classification of functioning, disability and health : ICF. 299 p.
6. World Health Organization. International classification of functioning, disability, and health : children & youth version : ICF-CY. World Health Organization; 2007. 322 p.
7. Mélo TR, Freitas J, Sabbag A de A, Chiarello CR, Neves EB, Israel VL. Intensive Neuromotor Therapy improves motor skills of children with Cornelia de Lange Syndrome: case report. Fisioterapia em Movimento. 2019;32.
8. Mariani M, Decimi V, Bettini LR, Maitz S, Gervasini C, Masciadri M, et al. Adolescents and adults affected by Cornelia de Lange syndrome: A report of 73 Italian patients. Am J Med Genet C Semin Med Genet. 2016 Jun 1;172(2):206–13.
9. Barisic I, Tokic V, Loane M, Bianchi F, Calzolari E, Garne E, et al. Descriptive epidemiology of Cornelia de Lange syndrome in Europe. Am J Med Genet A. 2008 Jan 1;146(1):51–9.
10. Bhatia R, Mehta DN. Cornelia De-Lange Syndrome: A Case Report. Int J Clin Pediatr Dent [Internet]. 2013 Aug;6(2):115–8. Available from: https://www.ijcpd.com/doi/10.5005/jp-journals-10005-1201
11. Rodríguez P, Asturias K. A 16-Day-Old Infant with a Clinical Diagnosis of Classical Cornelia de Lange Syndrome. Case Rep Pediatr. 2020 Apr 9;2020:1–4.
12. Cheng IF, Kuo LC, Lin CJ, Chieh HF, Su FC. Anthropometric Database of the Preschool Children from 2 to 6 Years in Taiwan. J Med Biol Eng. 2019 Aug 5;39(4):552–68.
13. Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, et al. Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. Vol. 143, American Journal of Medical Genetics, Part A. Wiley-Liss Inc.; 2007. p. 1287–96.
14. Mikołajewska E. Functional abilities in children with Cornelia de Lange syndrome – pilot study. Annales Academiae Medicae Silesiensis. 2019 Oct 22;73:199–202.
15. Mikolajewska E. Interdisciplinary Therapy in Cornelia de Lange Syndrome-Review of the Literature. Adv Clin Exp Med. 2013;22(4):571–7.

16. Kline AD, Barr M, Jackson LG. Growth Manifestations in the Brachmann-de Lange Syndrome. Vol. 47, American Journal of Medical Genetics. 1993.
17. Kline AD, Stanley C, Belevich J, Brodsky K, Barr M, Jackson LG. Developmental Data on Individuals With the Brachmann-de Lange Syndrome. American Journal of Medical Genetics. 1993.
18. Griffith GM, Hastings RP, Nash S, Petalas M, Oliver C, Howlin P, et al. "You have to sit and explain it all, and explain yourself." mothers' experiences of support services for their offspring with a rare genetic intellectual disability syndrome. J Genet Couns. 2011 Apr;20(2):165–77.
19. Cacioppo CN, Conway LJ, Mehta D, Krantz ID, Noon SE. Attitudes about the use of internet support groups and the impact among parents of children with Cornelia de Lange syndrome. Am J Med Genet C Semin Med Genet. 2016 Jun 1;172(2):229–36.
20. Kepala Badan Penelitian dan Pengembangan dan Perbukuan P, Pendidikan Kebudayaan K, dan Teknologi Anindito Aditomo Kepala Pusat Kurikulum dan Perbukuan Badan Penelitian dan Pengembangan dan Perbukuan Kementerian Pendidikan R, dan Teknologi Maman Fathurrohman Penanggung Jawab Koordinator Substansi Pengembangan Kurikulum Badan Penelitian dan Pengembangan dan Perbukuan Kementerian Pendidikan R, dan Teknologi Yogi Anggraena R. PANDUAN PELAKSANAAN PENDIDIKAN INKLUSIF. 2021.