

Case Report**Multiple Congenital Anomalies: Meningoencephalocele, Labiopalatoschisis and Clubfoot with Normal Chromosomal Analysis*****Multipel Kongenital Anomali : Meningoensefalokel, Labiopalatoskhizis, dan Kaki Pengkor dengan Hasil Analisis Kromosom Normal*****Sefty M. Samosir, Angghea Rachmiawaty, Ita Fatati, Alamsyah Aziz**

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Abstract

Objective: To perform chromosomal microarray when similar case was found.

Methods: Case report.

Case: G1P0A0, 20 years-old, 23-24 weeks gestation, normal BMI, was diagnosed by ultrasonography with multiple congenital anomaly consisted by meningoencephalocele, labiopalatoschisis, and clubfoot. Amniocentesis was performed to manage karyotyping analysis and a result of 46 XY was obtained. Neonate was delivered with exact condition according to prenatal diagnosis and was demised 6 hours postnatal. Patient had no history of smoking or DM, and no familial congenital deformity. Patient was a worker in textile manufactory and inadequacy folic acid intake during pregnancy was known. Early suspicion of aneuploidy as cause of multiple congenital anomalies in this case was not proven otherwise. Serology test also found no congenital infection. Literature research indicated tendency of MTHFR polymorphisms. Genetic analysis such as chromosomal microarray to establish involvement of MTHFR polymorphism is needed.

Conclusion: This case should behold as clinicians' consideration to perform additional examination and patients counseling when similar anomaly was found during prenatal ultrasonography examination.

Keywords: chromosomal microarray, karyotyping; MTHFR polymorphism, multiple congenital anomaly.

Abstrak

Tujuan: Untuk melakukan pemeriksaan kromosom microarray pada kasus yang sama.

Metode: Laporan kasus.

Kasus: G1P0A0, usia 20 tahun, hamil 23-24 minggu, didiagnosis secara ultrasonografi dengan kelainan kongenital multipel berupa meningoensefalokel, celah bibir-palatum, dan kaki pengkor. Amniosentesis dilakukan pada pasien untuk analisis kromosom dan didapatkan hasil 46 XY. Bayi lahir dengan kondisi yang sama dengan diagnosis prenatal tersebut dan meninggal 6 jam setelah melahirkan. Dari hasil anamnesis dan pemeriksaan kami dapatkan pasien bukan perokok, tidak ada keluarga dengan cacat bawaan, indeks masa tubuh pasien normal. Pasien merupakan karyawan pabrik tekstil dan pasien tidak mengkonsumsi asam folat adekuat selama kehamilan. Dua data terakhir yang kemungkinan berkontribusi terjadinya kelainan kongenital multipel pada kasus ini, yaitu kontak dengan teratogen dan defisiensi asam folat. Dugaan awal kelainan kromosom sebagai penyebab kelainan kongenital multipel pada kasus ini tidak terbukti. Sayangnya, investigasi-investigasi lebih lanjut berupa analisis genetik, seperti pemeriksaan apakah terdapat polimorfisme MTHFR yang berhubungan dengan defisiensi asam folat pada kasus ini tidak dilakukan karena keluarga pasien menolak.

Kesimpulan: Kasus ini sebaiknya menjadi bahan pertimbangan klinisi untuk melakukan pemeriksaan tambahan dan edukasi ke pasien pada saat menemukan kelainan yang sama pada pemeriksaan ultrasonografi prenatal.

Kata kunci: Mikroarray kromosom; karyotyping; multipel kongenital anomali; polimorfisme MTHFR.

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INTRODUCTION

Congenital anomaly is defined as structural, functional, or metabolic abnormality occurred during parturition which may result in physical disability or even death. Congenital anomaly contributes a reasonable proportion as neonatal death cause. In 2007, congenital anomaly was attributed to 1.4% of neonatal death,¹ which rose into 10.5% in 2010.² Congenital malformation as one major cause of congenital anomaly contributes to 5.7% of infant mortality and 4.9% of below-five-years-old children mortality. WHO-SEARO data in 2010 stated that hereditary disorder prevalence in Indonesia had reached 59.3 per 1000 livebirths.³

Major causes of congenital anomaly are genetic, infection, and environmental factors. A study conducted in Indonesia during January 2011 – June 2013 on 103 congenital malformation cases regarding chromosomal analysis test in Medical Biology Department, Faculty of Medicine Universitas Indonesia, concluded that 98.2% of congenital malformation cases was due to chromosomal abnormality.⁴ Thus, genetic modality raise an important role in establishing congenital anomaly causes.

CASE

A 20-year-old female, G1P0A0, 23-24 weeks gestation was referred to Feto-Maternal Medicine Division, Dr Hasan Sadikin General Hospital Bandung due to a suspicion to congenital anomaly. History taking revealed background of patients as textile manufactory worker. Patient had no history of smoking and had no history of diabetes mellitus. No family history of congenital deformity history was found. Body mass index was normal. Patients admitted that folic acid supplementation was only managed in first three months of gestation. Ultrasonography examination performed by Feto-Maternal Medicine Division revealed ventricle dilatation and cerebral falx shifting, accompanied by anterior and posterior cranial defect with size of 2.5 cm each with visible protruding brain tissue indicating an impression of meningoencephalocele. Facial region USG revealed a labiopalatoschisis, while extremity region USG revealed clubfoot (Figure 1).

Aneuploidy was suspected promptly as a cause of multiple congenital anomalies in this report. Amniocentesis were then done and resulted in 46XY.

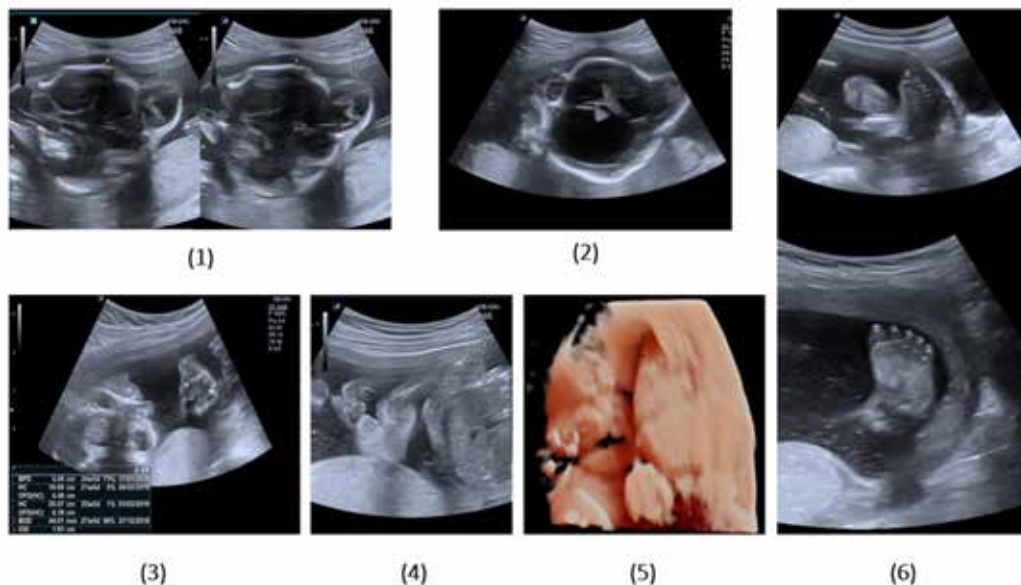


Figure 1. Ultrasonography test results. (1) and (2) indicating anterior and posterior meningoencephalocele. (3) interorbital distance of 1.83 cm. (4) and (5) labiopalatoschisis. (6) clubfoot

The baby was delivered precisely with prenatal diagnosis and was demised 6 hours postnatal (Figure 2). Cordocentesis were conducted perinatally to confirm chromosomal analysis results and identical 46XY result was found.



Figure 2. Perinatal condition of neonate. (1) labiopalatoschizis (2) labioplastoschisis and anterior meningoencephalocele. (3) posterior meningoencephalocele (4) and (5) clubfoot (6) overall neonate figure

Infection resulting a congenital anomaly was also suspected and serology test were conducted. However, no congenital infection was found (Table 1).

Table 1. Fetal Umbilical Cord Blood Examination Results

Anti-Toxoplasma IgG	< 0.50 IU/mL
Anti-Toxoplasma IgM	0.33 INDEX (nonreactive)
Anti-Rubella IgG	247.48 IU/mL (reactive)
Anti-Rubella IgM	0.28 INDEX (nonreactive)
TPHA	Nonreactive

DISCUSSION

Determining cause of congenital anomaly may be established by observing anomaly pattern according to prenatal development phases.⁵ Teratogenicity from either genetic or environmental cause on first 2 weeks following conception would likely result in embryonic demise rather than a malformation. Three to eight weeks following conception is an embryonic period of organogenesis, thus most of major malformation was presented in this critical period. Late prenatal development phase as in third months to delivery; which is also identified as fetal period, is a period when somatic growth and tissue maturation occurred. In this fetal period, morphological abnormalities finding would likely to be minor.

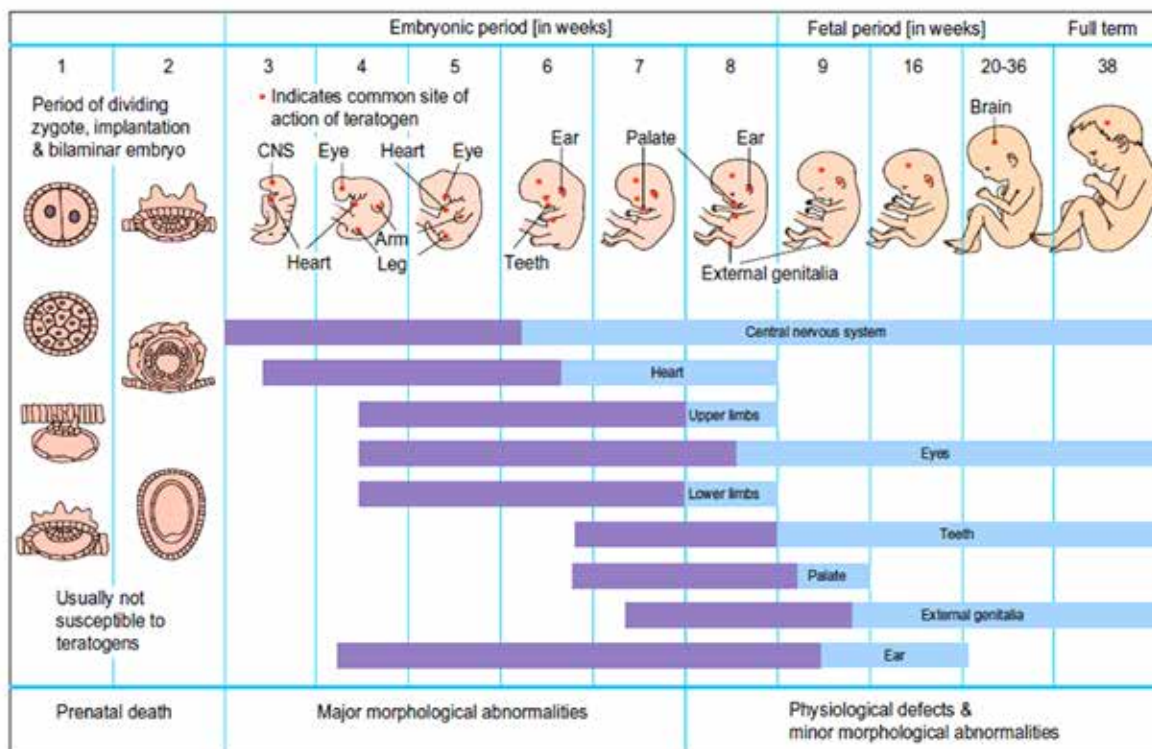


Figure 3. Critical Period from Prenatal Development Phases. Color of violet indicating most sensitive periods. Homfray and colleague.⁵

In this case, according to prenatal development phases, multiple congenital malformation was most probably occurred due to disorder in embryogenesis period, which ensued in third to eight weeks in gastrulation and neurulation process.⁶

There are two points suspectedly contributing in multiple congenital disorder in this patients, which are teratogen contact since patients occupation as textile manufactory worker, and folic acid deficiency according to patient acknowledgment that folic acid supplementation was managed only in the first three months of gestation. Association of maternal working environmental exposure stated that textile manufactory worker possessed risk to suffer from congenital anomaly as in NTD as much as 0.8x, labiopalatoschisis as much as 1.9x, and extremities reduction including clubfoot as much as 1.4x.⁷

Literature research was conducted to explore each cause of congenital anomaly in this cases and its associations then. Literature research indicated tendency of MTHFR (Methylenetetrahydrofolate Reductase) polymorphisms, which are MTHFR A1298C and C677T.⁸⁻¹⁰

Data from study conducted in Institut Pertanian Bogor in 2017 revealed that 88.3% pregnant women in Indonesia was classified as

folic acid deficiency state.¹¹ In this case, even if folic acid supplementation was inadequate during pregnancy, maternal folic acid serum level reveals normal results of 24.2 ng/mL. On the other hand it does not eliminate suggestion of MTHFR polymorphism in this case per se.

MTHFR is a key enzyme in human body compulsory in DNA synthesis and DNA methylation process.¹² MTHFR gene mutation in form of polymorphism will inhibit the enzyme activity, which constrain 5,10 methylene THF alteration into its active form of 5-MTHF (L-methylfolate), which is a common folate derivative found in circulation and major dietary folate form.¹³ Active 5-MTHF form is vital to convert homocystein into methionin by 1 carbon donation.

Every individual possess two copy of MTHFR gene, one is inherited from paternal side and the other one is inherited from maternal side. MTHFR gene mutation may occur on one or both gene copy.¹⁴ In this case, even though maternal folic acid serum level was found to be normal, MTHFR polymorphism might be occurred on paternal side which subsequently inherited to the fetus. To establish involvement of MTHFR polymorphism in this study, genetic analysis test on both parents and fetus are compulsory to be done, such as chromosomal microarray or *Single Nucleotide Polymorphism (SNP)*- array.¹⁵

CONCLUSION

This case report aims to be clinicians' consideration to perform additional examination and counseling into patients and her family when such similar anomaly finding was found on prenatal ultrasonography.

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