Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.65, No.4(2025). p.350-6 ; DOI: https://doi.org/10.14238/pi65.4.2025.350-6

Case Report

Edwards Syndrome and Trisomy 8: a case report of a newborn with multiple congenital anomalies with double aneuploidy

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Chromosomal aneuploidy is the most common genetic cause of multiple congenital anomalies (MCA), contributing to high neonatal mortality and morbidity rates in intensive care units. Prevalence of live birth double trisomy is rarely reported, with previous studies reporting the involvement of autosomal aneuploidy combined with sex chromosomal aneuploidy that is a more tolerable or benign phenotype. Mostly, a live-born baby with a double trisomy is associated with mosaicism. This report aims to present a rare case of a viable baby with non-mosaic double autosomal trisomy involving chromosomes 8 and 18. A term baby from advanced maternal and paternal age with low birth weight and height was born from spontaneous vaginal delivery from unremarkable pregnancy. The phenotype was suitable with Edward syndrome with congenital heart anomalies confirmed by cytogenetic analysis with additional extra chromosome 8 (48, XX,+8,+18). The baby was on and off the mechanical ventilator due to respiratory failures, and her health condition gradually deteriorated, leading to her death at the age of 2.5 months due to neonatal pneumonia. **[Paediatr Indones. 2025;65:164-70; DOI: https://doi.org/10.14238/pi65.6.2025.164-70**].

Keywords: double trisomy; trisomy 8; trisomy 18; multiple abnormalities; rare diseases

Double aneuploidy in a newborn baby is very rare because it is presumed not viable in most cases due to multiple organ anomalies, called multiple congenital anomalies (MCA). The most common genetic cause of MCAs are chromosomal and single-gene disorders, chromosomal abnormalities (structural and numerical) were found in approximately 40% of cases.[1] Previous studies reported as much as 50% of cases were related to genetic disorders.[2,3] There was a wide variation in the incidence over time and between countries (10% to 36.6%), reflecting multiple factors that may contribute to the incidence such as healthcare providers' knowledge and awareness, healthcare facilities (to detect prenatally and possibility to do termination), socio-cultural and religious beliefs, control of infection, and nutritional deficiency.[4-6]

Neonates with MCA contribute considerably to the mortality rate (34%) in neonatal intensive care units (NICU).2 Previous live-born cases have been reported involving sex chromosomes combined with autosomal aneuploidy, mostly trisomy 13, 18, or 21.[7,8] Extra sex chromosomes are more tolerable in humans than autosomal trisomies, and sex chromosome trisomies are generally benign. It primarily affects sexual development and fertility, but they often have normal life spans, while autosomal aneuploidy is mostly deleterious.[9] Rare autosomal trisomies (RATs) are chromosomal trisomies besides involving chromosomes 13, 18, 21, X, and Y, in complete/non-mosaic form, RATs are usually lethal

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Submitted March 26, 2023. Accepted January 3, 2025.

or not compatible with life and they have therefore infrequently been found as a result of invasive prenatal diagnosis from amniotic fluid or chorionic villus cells. While, in mosaic form, RAT has been linked with fetal death, stillbirth, intrauterine growth restriction (IUGR), MCA, and minimally affected individuals.[10] In principle, a RAT is only viable when present in mosaic state.

The origin of numerical chromosomal abnormalities/aneuploidy are meiotic and mitotic errors. Failure of homolog chromosomes to segregate properly to opposite poles during telophase, called meiotic non-disjunction, results in the production of gamete with improper chromosome number in complete form. When a normal gamete combines with a gamete with an extra chromosome, resulting a trisomy zygote.[11] Predominantly in female meiosis, although there is discrepancy among different chromosomes, these increase exponentially in women over the age of 35 years, called advanced maternal age.[12] Postzygotic mitotic non-disjunction (error in chromosome segregation during mitosis) during early embryonic development accounted as the origin of mosaic form.[13]

We present a live-born baby with multiple congenital anomalies suspected to have Edward syndrome with double autosomal trisomies (48, XX,+8,+18) karyotype.

The case

A female baby was born at term to a 41-year-old gravida 3, para 2, abortus 0 mother from an unremarkable pregnancy and advanced paternal age (41-year-old). She was delivered with spontaneous vaginal delivery, her weight was 1700 g, the birth length was 42 cm (< 3rd centile), microcephaly (<3rd centile), and birth asphyxia (**Figure 1**). Physical examination showed microcephaly, microphthalmia, hypertelorism, a depressed nasal bridge, low-set ear, micro-retrognathia, and high-arched palate. The sternum was short with pectus excavatum, wide set nipple, and the heart examination presented a systolic murmur. No liver and spleen enlargement. Genitalia was a typical female. The extremities examination showed clenched hands with overlapping fingers, single palmar transverse crease, prominent calcaneus, and talipes equinovarus.

Figure 1. Patients at 1-month-old. Note: microphthalmia, depressed nasal bridge, low set ear, micrognathia, and short sternum

She had mild hyponatremia (130-135mmol/L, reference: 136-145mmol/L).

An Echocardiogram demonstrated a moderate perimembranous ventricular septal defect and a small secundum atrial septal defect (ASD II). A cranial ultrasound revealed no intraventricular hemorrhagic and no enlargement in the ventricles. Renal ultrasound was unremarkable. Laboratory evaluation showed hemoglobin level was 8.9 g/dL. Cytogenetic analysis showed a karyotype of 48 XX,+8,+18 (**Figure 2**).

She was admitted to the neonatal intensive care unit on 2nd day after birth and used a mechanical ventilator for two weeks due to poor respiratory effort, and she has been on and off the mechanical ventilator since then. She also had a problem with frequent vomiting, neonatal jaundice, anemia, and pneumonia. Her clinical course was marked by multiple organ failure. The first resuscitation was succeeded in the last hospitalization in the pediatric intensive care unit. Parents were educated regarding their child's condition and the prognosis; subsequently, the parent was made a do not resuscitate (DNR) decision. She died at 2.5 months of age due to neonatal pneumonia. Clinical characteristics of this patient are in concordance with Edwards syndrome and Trisomy 8, with the details listed in **Table 1**.

Discussions

We presented, to the best of our knowledge, the first liveborn baby with double aneuploidy of chromosomes 18 and 8 worldwide. Another double aneuploidy of autosomes was reported in a previous study which found trisomy 7 and 8 from a case of spontaneous abortion.[14]

The case was born from advanced maternal and paternal age. In most cases, advanced maternal age is the most common risk factor for meiosis non-disjunction, the origin of numerical abnormalities called aneuploidy.[15] Chromosome segregation errors in meiotic I due to premature centromere division and defective spindle assembly checkpoint at meiosis I increase dramatically in women age, from around 2-3% in a woman in her 20s and dramatically increases to about 35% in a woman in her 40s.[12,15,16] However, the origin of autosomal aneuploidy specific patterns exists.

Trisomy 18, called Edwards syndrome, is the second most common type of aneuploidy, with a prevalence of 1 in 2,000 to 8,000 live births and a male-female ratio of 5:1.[17-19] Most human aneuploidies found in embryos originate from the egg.[20,21] In the previous parental study, the maternal origin was 95%, and the remaining cases were

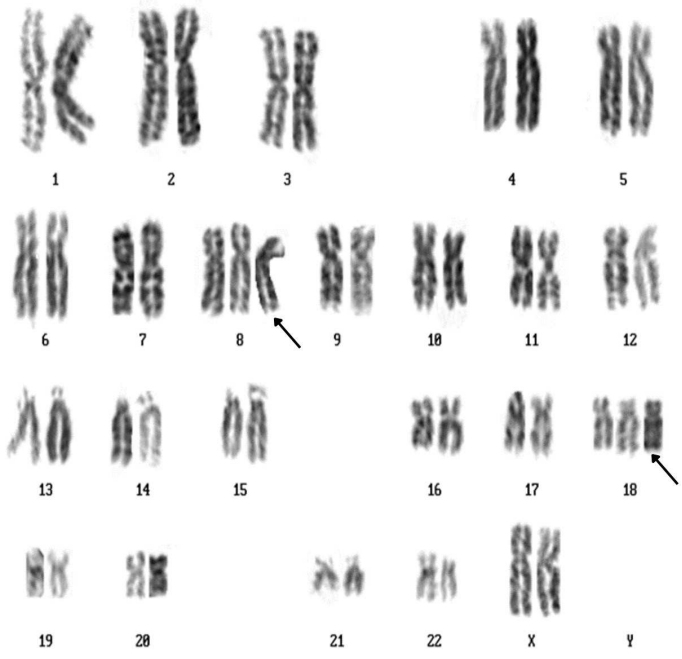

Figure 2. Karyotype revealed double trisomy (48 XX, +8, +18)

Table 1. Clinical characteristics of case according to trisomy 8 and 18

Clinical characteristics	Trisomy 8	Trisomy 18	Our Case
Neurological anomalies			
Hypotonia		+	-
Seizure		+	-
Poor sucking		+	N/A
Developmental delay	+	+	+
Craniofacial anomalies			
Microcephaly		+	+
Prominent occiput		+	-
Prominent forehead	+		-
Triangular Face		+	+
Asymmetric face		+	+
Microphthalmia		+	+
Deeply set eyes	+		-
Hypertelorism	+	+	+
Epicanthal folds		+	+
Micro-retrognathia	+	+	+
Incomplete dental occlusion	+		N/A
Cleft lip and palate		+	-
High palate	+		
Small and triangular mouth	+		Small mouth +
Downturn mouth	+		-
Shallow philtrum	+		+
Prominent malar bone	+		-
Microtia		+	-
Thickened helix	+		-
Deep conchae	+		+
Low set ear		+	+
Strabismus	+		-
Ear dysplasia		+	+
Hypoplastic nasal root		+	-
Prominent nasal bridge		+	+
Broad nasal bridge	+		+
Upturn nose/everted nostril	+	+	+
Choanal atresia		+	N/A
Low anterior hairline	+		-
Musculoskeletal anomalies			
Severe growth retardation		+	+
Generalized atrophy	+		-
Short stature	+		+
Short neck	+	+	-
Webbed neck	+		-
Short sternum		+	+
Pectus excavatum		+	+
Barrel chest	+		-

Table 1. Clinical characteristics of case according to trisomy 8 and 18 (continued)

Clinical characteristics	Trisomy 8	Trisomy 18	Our Case
Wide set nipple		+	+
Clench hand with overriding fingers		+	+
Rocker bottom feet with prominent calcaneus		+	+
Deep plantar creases	+		N/A
Talipes equinovarus		+	+
Joint contracture	+		-
Kyphoscoliosis	+		-
Absent/dysplastic patella	+		N/A
Generalized osteoporosis	+		-
Cardiovascular anomalies			
Ventricular septal defect		+	+
Atrial septal defect		+	+
Patent ductus arteriosus		+	-
Tetralogy of Fallot		+	-
Pulmonary anomalies			
Pulmonary hypoplasia		+	-
Laryngomalacia		+	-
Gastrointestinal anomalies			
Omphalocele		+	-
Atresia esophageal		+	-
Pyloric stenosis		+	-
Umbilical hernia		+	-
Genitourinary anomalies			
Horseshoe kidney		+	-
Renal agenesis		+	-
Clitoral hypertropia		+	-
Central nervous system anomalies			
Hydrocephalus		+	-
Corpus callosum hyperplasia	+	+	-

paternal origin.[22] Meiosis II non-disjunction error is the predominant mechanism of trisomy 18, where advanced maternal age is the jeopardy. [23] The average lifespan for infants with trisomy 18 is three days to two weeks; 5-38% survive for three months.[24] Survival rate is greatly affected by trisomy 18; only 10% of cases with this condition will survive beyond the first year of life because it involves multiple organs and systems.[25] The main clinical characteristics of Edwards syndrome are mostly observed in this case, which are developmental delay, congenital heart disease, growth retardation, microcephaly, triangular and asymmetric face, microphthalmia, hypertelorism, low set ears, prominent nasal bridge, upturned nose, micro-retrognathia, clenched fist with overlapping fingers, and rocker bottom feet,[26] hence, supporting the clinical diagnosis.

Trisomy 8 is a rare condition, comprising 0.7% of spontaneous abortions.[27] In live-born, trisomy 8 is almost always associated with mosaicism. Non-mosaic cases, trisomy 8 cases mostly lead to adverse pregnancy outcomes from pregnancy loss to spontaneous abortion.[28] In most spontaneous abortion cases, the additional chromosome was due to maternal meiosis non-disjunction, while a post-zygotic mitotic gain of the additional chromosome was molecularly proven in liveborn cases.[23,28] Individuals with complete trisomy 8 are considered fatal; thus, individuals in whom an

extra chromosome 8 is believed to be always mosaic trisomy. In the absence of serious malformations, the survival rate is considered high. Trisomy 8 mosaicism (T8M), called Warkany syndrome 2 is an enormously infrequent chromosomal abnormality in newborn babies with a prevalence of approximately 1: 25,000-50,000.[19] Characteristics of T8M are also extremely variable ranging from severe congenital malformations such as skeletal abnormalities (principally vertebral and costal alterations), facial dysmorphisms, typically deep palmar and plantar creases, and developmental delay/intellectual disability to minute dysmorphic or normal individuals,[29] thus, this condition often goes undiagnosed. Identifying cases of partial or complete trisomy 8 mosaicism using lymphocytes of peripheral blood conventional karyotyping is very challenging; in most cases, alteration is only found in fibroblasts.[30] In our case, we found trisomy 8 from the peripheral blood lymphocytes using conventional karyotyping.

Aneuploidy in the resulting egg and embryo leads to adverse pregnancy outcomes ranging from pregnancy loss, stillbirth, and multiple congenital anomalies or neonatal mortality.[31] The earlier pregnancy loss, the higher the rate of the chromosomal defect; only approximately 10% of aneuploidy embryos will reach ≥ 20 weeks of pregnancy and be born with MCA, stillbirth, or neonatal death.[32] Chromosomal testing is still an option to confirm aneuploidy in a patient with MCA, especially in limited-resources settings. Double trisomy is a very rare chromosomal aberration that may cause adverse pregnancy outcomes from pregnancy loss to live birth babies with MCA, and the origin of additional autosomal aneuploidy is a specific pattern.

Limitation of study. Diagnosis was done using conventional karyotype, in which the low level of mosaicism may not be detected. Fluorescent in situ hybridization (FISH) can be used and successfully identify a low level of mosaicism.

Although very rare, this case shows that numerical chromosomal abnormalities may involve more than one autosome, called double trisomies, especially in children with major congenital abnormalities. Care should be taken to ensure other aneuploidy is not missed.

Conflict of interest

None declared.

Funding acknowlegment

This work was supported by World Class Research University grant from Universitas Diponegoro [No. 118-02/UN7.6.1/PP/2021].

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