Second-trimester prenatal diagnosis of trisomy 18 associated with elevated maternal serum alpha-fetoprotein level, bilateral multiple choroid plexus cysts, cleft lip and palate, and atrioventricular septal defect, and review of the literature

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Research

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Abstract

Objective: To present the prenatal diagnosis of trisomy 18 and to review of the literature.

Case: A 29-year-old pregnant woman was showed high risk of trisomy 18 by maternal serum screening at 16 weeks' of gestation, showing elevated AFP(125 U/mL, 3.25 MoM), low free β -hCG (3.29 ng/mL, 0.11 MoM), low PAPP-A (1120 mU/L, 0.31 MoM). She asked for an amniocentesis because the risk value for trisomy 18 was 1/5 and trisomy 21 was 1/77121. **Results:** The results of amniocentesis on Prenatal BoBs revealed a fetus with trisomy 18, whose karyotype of amniotic fluid cells was 47, XY, +18. Ultrasonography demonstrated intrauterine pregnancy, single live fetus, multiple abnormalities including "strawberry head ", bilateral multiple choroid plexus cysts, cleft lip and palate, and atrioventricular septal defect. The pregnancy was terminated subsequently.

Conclusion: Trisomy 18 can be identified in prenatal screening with advanced maternal age, abnormal maternal serum screen results, and multi-structural abnormal ultrasonography results. Fetuses with trisomy 18 may be associated with congenital heart disease, neural tube malformation, abdominal valgus, omphalocele, multiple cysts in bilateral choroid plexus, cleft lip and palate, elevated AFP, and decreased free β -hCG and PAPP-A.

Introduction

Trisomy 18, also called Edwards syndrome (ES), is the second-most common autosomal trisomy syndrome [1]. The prevalence of trisomy 18 infants born alive rang from 1/6000 to 1/8000. As most of fetuses with trisomy 18 are spontaneously aborted or artificially terminated during gestation, the incidence of trisomy 18 is much higher than the current statistics, which was about 1/2500 to 1/2600[1]. Trisomy 18 is generally caused by the nondisjunction of chromosome 18 during meiosis of maternal germ cells, including complete and mosaic trisomy 18 [2].

The clinical manifestations of fetuses with trisomy 18 are complex and varied, including mental development abnormalities, multiple and severe structural abnormalities. Ultrasonography often show atrioventricular septal defect, "strawberry head ", choroid cyst, cleft lip and palate, single umbilical artery, hook hand, etc [2–4]. As two non-invasive screening techniques, pregnancy serological screening and fetal ultrasound screening have been widely used in the screening of trisomy 18 and other chromosomal abnormalities recently. Previous studies confirmed that pregnancy related plasma protein A (PAPP-A), alpha fetoprotein (AFP) and free human chorionic gonadotropin β -subunit (free β -hCG) in maternal serum with trisomy 18 were lower than normal pregnant women. We found a case of fetus with trisomy 18 with elevated AFP in maternal serum. Here, we present such a case and review of relevant literature.

Case Report

A 29-year-old pregnant woman, gestation 2 delivery 0, presented to us with BOBs in amniotic fluid indicating trisomy 18 of the fetus at 20 weeks and 5 days of gestation. She was normally in good health,

with regular menstruation. There was no difference in this pregnancy and no vaginal bleeding after menopause. She did not receive folic acid supplements regularly, and she had mild pregnancy reactions and had a medical abortion one year ago. She had no history of viral infection, no history of radiation exposure, no history of tobacco or alcohol exposure, no history of house decoration, no history of chemical exposure. The risk values of first-trimester maternal serum screening for trisomy 18 was 1/5. The results of NT in early pregnancy showed fetal nuchal translucency thickness was 2.6 mm, crown-rump length (CRL) 5.8 cm and visible nasal bone.

At 12 weeks and 2 days of gestation, the results of maternal serum screen presented PAPP-A (1120 mU/L) of 0.31 MoM, Free β -hCG (4.21 ng/mL) of 0.07 MoM, NT (2.6 mm) of 1.95 MoM, T21 risk value 1/10160, T18 risk value 1/16. Combined first and second trimester maternal serum screening results at 16 weeks of gestation showed AFP (125 U/mL) of 3.52 MoM, Free β -hCG (2.39 ng/mL) of 0.11 MoM, T21 risk value was 1/77121 and T18 risk value was 1/5.

At 21 weeks' of gestation, 3D ultrasound showed many abnormalities: the gestational age of the fetus was consistent with the actual gestational age and the head shape was slightly like "strawberry head" (Fig. 1). multiple cystic dark areas were seen in the bilateral choroid plexus and the larger one was on the right side about 1.3*0.9*0.6 cm in size (Fig. 2). the echo interruptions about 0.2 cm were observed in the upper lip and the upper alveolar echo was discontinuous (Fig. 3). the upper of ventricular septum and atrial septum were not shown (Fig. 4). The Ultrasonic diagnosis was intrauterine pregnancy, single live fetus, "strawberry head", bilateral multiple choroid plexus cysts, cleft lip and palate, atrioventricular septal defect.

After amniocentesis, the fetus was identified with trisomy 18 by Prenatal BoBs testing, and no aneuploidy of 13, 21, X and Y chromosome and no abnormal deletion of Prader-Willi/Angelman and other chromosomal microdeletion syndrome were found (Fig. 5). The karyotype of the fetus was 47, XY, + 18 (Fig. 6).

With the consent of the pregnant woman, the pregnancy was terminated at 21 weeks and 2 days of gestation with prostaglandin applied to the cervix of the woman. A male stillbirth corresponding to the gestational age was delivered vaginally, weighing 292 g and measuring 23 cm in length. The proband postnatally manifested strawberry head, a cleft lip and palate and the fetal membrane was basically complete. This study was approved by the medical ethics committee of the Hangzhou Women's Hospital [2020] Medical Ethics Review A (10) -11.

Discussion

Chromosomal abnormalities are a major cause of perinatal infant death and disability. After Down syndrome, trisomy 18 is the second most common autosomal trisomy disease. Recently, the incidence of trisomy 18 has an increasing trend due to the wide use of prenatal screening and prenatal diagnosis [5]. The older the pregnant women, the higher the incidence of trisomy 18 [6]. The prognosis of trisomy 18 after delivery is poor. Even if lucky enough to survive, their median survival is only 3–6 days, with less

than 50% of babies surviving for a week and only about 5–10% surviving for one year [7]. Fetuses with complete trisomy 18 have severe multiple malformations, while mosaic trisomy 18 have lighter clinical manifestations and longer survival time. There was a report about a girl more than 26 years old with trisomy 18, she was in stable condition but repeatedly infected respiratory system diseases [8]. In fetuses with trisomy 18, Robert et al.[9] found that the surviving female infants (61.2%) were much higher than male infants (38.8%), and the mortality was related to gestational age, and omphalocele and heart defects increased the risk of death of infants with trisomy 18. Studies of KVista's were similar to this [10].

AFP is a glycoprotein, often referred to as fetal albumin, produced by the yolk sac of the embryo, the fetal liver and gastrointestinal system. Physiological synthesis of AFP in fetal liver gradually increase from 20 weeks of gestation and reach a stable state at 32 weeks. AFP is excreted into the amniotic fluid by fetus's urine, and then spread across the placenta to the maternal serum [11]. In 1972, British scientists were the first to recognize that high AFP level could be used to diagnose neural tube malformations in fetuses [12]. Later, a large number of data found that low AFP level in maternal serum was associated with trisomy 21 and trisomy 18, and thus it was used for prenatal screening for autosomal trisomy disease. Yamamoto et al. [13] proved that AFP in the maternal serum with trisomy 21 and trisomy 18 was lower than that of normal pregnant women, and AFP MoM was lower in trisomy 18 than trisomy 21. Geyl et al. [14] also showed that high AFP was a marker for neural tube defect or abdominal wall defect, while low AFP indicated high risk of trisomy 18. However, the AFP level in this case was found to be abnormally high, reaching 3.52 MoM. We found that less data regarding related literature is available. Lindenbaum [15] showed that fetuses of trisomy 18 in the absence of neurological dysplasia, the maternal serum AFP level was significantly reduced during the second trimester (0.6 MoM), whereas it was increased in the presence of nervous system dysplasia (4–5 MoM), and we speculated that increased AFP may be related to the developmental defects of fetuses with trisomy 18. The fetus in this case had multiple abnormalities such as bilateral choroid plexus multiple cysts, cleft lip and palate, atrial septal defect, which may cause AFP to be continuously released into the maternal blood from the lesion rupture. Therefore, in order to higher detection rate of chromosomal diseases, the risk model of prenatal maternal serum screening should be adjusted according to specific situation. In order to prevent missed detection, we should not only focus on the risk value, but also individual MoM anomalies in the future work.

In this case ultrasonography demonstrated atrioventricular septal defection, bilateral multiple choroid plexus cysts, cleft lip and palate and strawberry head. Detailed ultrasonography screening is of great clinical significance to find fetuses with trisomy 18 and other chromosomal abnormalities. Studies have shown that the detection rate based on maternal serum screen and ultrasonography for chromosomal abnormal diseases is as high as 92.7%, which is far higher than that of solely maternal serum screening and ultrasonography screening [16]. Approximately 80–100% of fetuses with trisomy 18 present with different forms of heart defects, the most frequently observed anomalies being atrioventricular septal defect, patent ductus arteriosus, and tetralogy of fallot [17–18]. On the plane of fetal head, strawberry head show sharpened frontal bone, flattened occipital bone and shortened occipital frontal diameter, which look like strawberry. Strawberry head is common in fetuses with trisomy 18. When this feature is found on ultrasound, other manifestations indicating abnormalities of trisomy 18 should be fully

examined, including choroid plexus cysts, congenital heart disease, diaphragmic hernia and foot deformities. Fetal choroid plexus cysts are pseudocysts filled with cerebrospinal fluid in the choroid plexus. Around 1–2% of fetuses are detectable in second-trimester normal pregnant women, with gradually disappearing after 26–28 weeks [18]. Studies have shown that choroid plexus cysts are closely associated with chromosomal abnormalities such as trisomy 21, 18. About 50% of trisomy 18 can be detected choroid plexus cysts. When the diameter of the cyst is more than 10 mm with bilateral or multiple cysts, we should pay close attention to chromosomal abnormalities [19]. The incidence of cleft lip and palate in live births is about 1/500–1/700, and it is one of the most common congenital craniofacial malformations in human beings, with ethnic and geographical differences. Studies have proved that the cleft lip and palate with chromosomal abnormalities are more serious and the prognosis is poor [20].

In conclusion, for pregnant women with high risk of maternal serum prenatal screening, fetal systematic ultrasonography should be performed, which will greatly improve the screening efficiency. If the maternal serum screening showing high risk or intermediate risk of trisomy 18 and systematic ultrasonography showing multiple structural abnormalities, invasive prenatal diagnosis is the best option. In the future work, we need to pay more attention to the increase or decrease of single index MoM value of serological screening.

Declarations

Ethics approval and consent to participate

The study was approved by Hangzhou Women's Hospital (Hangzhou Maternity and Child Health Care Hospital) ethics committee, in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. And the approval number was [2020] Medical Ethics Review A (10) -11. Patients' consents were not required because this was a retrospective study.

Consent for publication

Not applicable; this was a retrospective study and no individual person's personal information is included.

Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts interest

No potential conflict of interest was reported by the authors.

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Author Contributions

Y.M. Chen design; Y.J. Chen and W.W. Ning wrote the first draft of the manuscript. L.Huai and A.Q. Huang, provision of study material or patients Ultrasonic diagnosis; L.Huai and Y.M. Chen performed laboratory measurements; Y.M. Chen, Y. J. Chen and W.W. Ning, writing-review & editing. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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References

- [1] Cereda Anna, Carey John C, The trisomy 18 syndrome. *Orphanet J Rare Dis*, 2012, 7: 81.
- [2] Rosa Rafael Fabiano M, Rosa Rosana Cardoso M, Zen Paulo Ricardo G, et al. Trisomy 18: review of the clinical, etiologic, prognostic, and ethical aspects. *Rev Paul Pediatr*, 2013, 31: 111-20.
- [3] Li Ting, Zhao Hanzhi, Han Xu, et al. The spontaneous differentiation and chromosome loss in iPSCs of human trisomy 18 syndrome. *Cell Death Dis*, 2017, 8: e3149.
- [4] Becker David A, Tang Ying, Jacobs Adam P, et al. Sensitivity of prenatal ultrasound for detection of trisomy 18. *J Matern Fetal Neonatal Med*, 2019, 32: 3716-3722.
- [5] Tonks A M, Gornall A S, Larkins S A, et al. Trisomies 18 and 13: trends in prevalence and prenatal diagnosis - population based study. *Prenat Diagn*, 2013, 33: 742-50.
- [6] Tian Chan, Deng Tao, Zhu Xiuhuang, et al. Evidence of compliance with and study of 189,809 cases. *Sci China Life Sci*, 2020, 63: 319-328.
- [7] Rasmussen SA, Wong LY, Yang Q, et al. Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics*. 2003. 111(4 Pt 1): 777-784
- [8] Alshami Abbas, Douedi Steven, Guida Melissa, et al. Unusual Longevity of Edwards Syndrome: A Case Report. *Genes (Basel)*, 2020, 11: undefined.
- [9] Meyer Robert E, Liu Gang, Gilboa Suzanne M, et al. Survival of children with trisomy 13 and trisomy 18: A multi-state population-based study. *Am J Med Genet A*, 2016, null: 825-37.
- [10] Crider Krista S, Olney Richard S, Cragan Janet D, Trisomies 13 and 18: population prevalences, characteristics, and prenatal diagnosis, metropolitan Atlanta, 1994-2003. *Am J Med Genet A*, 2008, null: 820-6.

- [11] Aboughalia Hassan, Bastawrous Sarah, Revzin Margarita V, et al. Imaging findings in association with altered maternal alpha-fetoprotein levels during pregnancy. *Abdom Radiol (NY)*, 2020, 45: 3239-3257.
- [12] Brock DJ, Sutcliffe RG. Alpha-fetoprotein in the antenatal diagnosis of anencephaly and spina bifida. *Lancet* 1972; 2:197-9.
- [13] Yamamoto R, Azuma M, Kishida T et al. Total alpha-fetoprotein and Lens culinaris agglutinin-reactive alpha-fetoprotein in fetal chromosomal abnormalities. *BJOG*, 2001, 108: 1154-8.
- [14] Geyl C, Subtil D, Vaast P, et al. [Interpretation of atypical values of maternal serum markers]. *J Gynecol Obstet Biol Reprod (Paris)*, 2014, 43: 5-11.
- [15] Lindenbaum R H, Ryyänänen M, Holmes-Siedle M et al. Trisomy 18 and maternal serum and amniotic fluid alpha-fetoprotein. *Prenat Diagn*, 1987, 7: 511-9.
- [16] Lai S, Lau W L, Leung W C, et al. Is ultrasound alone enough for prenatal screening of trisomy 18? A single centre experience in 69 cases over 10 years. *Prenat Diagn*, 2010, 30: 1094-9.
- [17] Albizua Igor, Chopra Pankaj, Sherman Stephanie L, et al. Analysis of the genomic expression profile in trisomy 18: insight into possible genes involved in the associated phenotypes. *Hum Mol Genet*, 2020, 29: 238-247.
- [18] Watson William J, Miller Richard C, Wax Joseph R, et al. Sonographic findings of trisomy 18 in the second trimester of pregnancy. *J Ultrasound Med*, 2008, 27: 1033-8; quiz 1039-40.
- [19] Bronsteen Richard, Lee Wesley, Vettraino Ivana M, et al. Second-trimester sonography and trisomy 18. *J Ultrasound Med*, 2004, 23: 233-40.
- [20] Gillham J C, Anand S, Bullen P J, Antenatal detection of cleft lip with or without cleft palate: incidence of associated chromosomal and structural anomalies. *Ultrasound Obstet Gynecol*, 2009, 34: 410-5.

Figures

Figure 1

Ultrasound expression of strawberry head

Figure 2

Ultrasound expression of Choroid plexus cyst

Figure 3

Ultrasound expression of cleft lip and palate

Figure 4

Ultrasound expression of atrioventricular septal defect

Expand All	Probe	Normalized Ratios		Threshold: 0.83-1.17					Threshold Y: 0.74-1.2				
		Sample/F	Sample/M	0.0	0.5	1.0	1.5	2.0	0.0	0.5	1.0	1.5	2.0
(5)	13C	1.07	1.03										
	18C1: 67 18p11	1.32	1.25										
	18C2: 68 18p11	1.24	1.22										
	18C3: 69 18q12	1.42	1.43										
	18C4: 70 18q21	1.48	1.46										
	18C5: 73 18q22	1.59	1.64										
(5)	21C	1.02	0.98										
(6)	AUTO	0.99	0.99										
(8)	CDC	0.99	0.98										
(4)	DGS	0.99	0.96										
(4)	DiG	1.01	1.00										
(7)	LGS	1.03	1.02										
(6)	MDS	0.98	0.92										
(7)	PWS	1.04	1.00										
(4)	SMS	0.98	0.93										
(5)	WBS	1.01	0.93										
(5)	WHS	1.02	0.96										

Figure 5

Results of Prenal Bobs testing on amniotic fluid cells

Figure 6

Karyotype of 47, XY, +18