How reliably does prenatal echocardiography predict urgent balloon atrial septostomy in fetuses with d-TGA?

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Abstract

Background: Transposition of the great arteries (TGA) is a conotruncal abnormality. It is associated with ventriculoarterial discordance with the parallel orientation of the great arteries, in which the aorta arises from the right ventricle to supply the systemic circulation, while the main pulmonary artery arises from the left ventricle to supply the pulmonary circulation. Aim: To analyze the prenatal and postnatal outcomes of fetuses with d-TGA and to determine whether prenatal echocardiography may predict postnatal urgent BAS. Methods: A retrospective study of fetuses with d-TGA, for which fetal echocardiography was performed at our tertiary hospital from January 2018 to May 2023. We assessed the appearance of the septum primum and the foramen ovale (FO) flap in the four-chamber view as to whether the FO had a restrictive appearance during measurement of the diameter of the FO at its maximal angle to the attachment point. Color Doppler was used to detect ventricular septal defects (VSD) and measure its diameter both in the four-chamber view and when visualizing the outlets of the great arteries in the sagittal section of the heart. Results: During the study period, 64 fetuses were diagnosed with d-TGA, which was also confirmed postnatally. Of these, 16 fetuses were excluded due to additional cardiac anomalies or the inability to reach the mother. In total, 48 cases were included in this series. In our study, the FO diameter was significantly decreased in the urgent BAS group, compared with the fetuses without urgent BAS (5.1 mm vs 6.3 mm, p?0.05). A cut off of 6 mm for the FO diameter (sensitivity, 73.3%; specificity, 72.2%; area under the curve [AUC], 0.764) and 3.2 mm for the VSD diameter (sensitivity, 75%; specificity, 75%; AUC, 0.728) suggested urgent BAS. The FO diameter and the presence of VSD were independent variables associated with urgent BAS in fetuses with d-TGA (p?0.05). Conclusion: Prenatal echocardiography in fetuses with d-TGA provides valuable information to estimate the need for postnatal urgent BAS that would prevent immediate life-threatening complications.

1 INTRODUCTION

Transposition of the great arteries (TGA) is a conotruncal abnormality, accounting for 5% to 7% of all congenital heart defects.[1] It is associated with ventriculoarterial discordance with the parallel orientation of the great arteries, in which the aorta arises from the right ventricle to supply the systemic circulation, while the main pulmonary artery arises from the left ventricle to supply the pulmonary circulation. The atrioventricular relationship remains normal, with each atrium connecting its corresponding ventricle. In the majority of cases (88%), the great vessel arrangement is malpositioned, in that the aorta lies anterior to and on the right side of the pulmonary artery forming a subaortic conus, while the pulmonary artery lies posterior to and on the left side of the aorta. This great vessel malposition is referred to as dexter-TGA (d-TGA). In d-TGA, the deoxygenated systemic venous blood is sent to the body through the aorta, and the oxygenated pulmonary venous blood is sent to the lungs through the main pulmonary artery. This condition is tolerated well during the fetal development because oxygenated and deoxygenated blood is mixed through the foramen ovale (FO) and ductus arteriosus (DA). After birth, d-TGA is associated with life-threatening cyanosis and hypoxemia in the presence of an intact ventricular septum (IVS), restricted FO and/or DA.[2]

Despite the advances in the diagnosis of prenatal TGA, its detection rate of still remains at 50%. Abnormalities of the FO and DA are encountered in about 20% of fetuses with d-TGA. Therefore, in addition to the prenatal diagnosis of d-TGA, detection of restricted FO and/or DA is essential, because the neonate is at an increased risk for hypoxemia and neonatal hemodynamic compromise after delivery due to the lack of compensatory mixing of blood. Such fetuses identified in the prenatal period are admitted to the neonatal intensive care unit (NICU) and treated immediately after birth with prostaglandin E (PGE) infusions to reopen and maintain the patency of the DA and/or, if required due to the persistence of hypoxia, and metabolic acidosis, by urgent balloon atrial septostomy (BAS) to improve hypoxia and allow time for an arterial switch operation.[3-5]

This study aims to analyze the prenatal and postnatal outcomes of fetuses with d-TGA and to determine whether prenatal echocardiography may predict postnatal urgent BAS.

2 MATERIALS AND METHODS

2.1 Study population

This is a retrospective study of fetuses with d-TGA, for which fetal echocardiography was performed at our tertiary hospital from January 2018 to May 2023. In this cohort, we included fetuses diagnosed with d-TGA on the second trimester ultrasonographic screening or referred to our hospital for confirmation of the diagnosis. Exclusion criteria included fetuses with congenitally corrected TGA, double-inlet left ventricle, atrioventricular septal defect, atrioventricular valve atresia, great artery stenosis-atresia, or any extracardiac anomaly. Fetuses with additional cardiac and non-cardiac anomalies were also excluded because they might adversely affect the postnatal hemodynamic status. Ventricular septal defects (VSD) were not considered a major cardiac anomaly. We only enrolled cases in which the last prenatal echocardiographic examination was performed within two weeks prior to delivery and whose ultrasonographic videos and images were available.

The study was approved by the ethics committee of Zeynep Kamil Women and Children Diseases Training and Research Hospital (Date and number: 24.05.2023/87) and was performed in compliance with the Declaration of Helsinki. Data retrieval and reporting conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

2.2 Fetal and maternal parameters

The follow-up data of fetuses with d-TGA were retrospectively retrieved from our hospital's electronic data system. All fetuses diagnosed with d-TGA were examined every two weeks until birth. During every ultrasonographic examination, the estimated birth weight, fetal biometry and amniotic fluid index were estimated, and umbilical artery Doppler measurements were made. Maternal age, gestational age at birth, mode of delivery, and birth weight were also recorded. Prenatal genetic testing for aneuploidies and 22q11 microdeletion was offered to all families.

2.3 Fetal echocardiographic and quantitative measurements

Fetal echocardiographic examination was performed with the heart in the anterior position. The right and left ventricular widths and lengths were measured at end-diastole in the four-chamber view. We assessed the appearance of the septum primum and the FO flap in the four-chamber view as to whether the FO had a restrictive appearance during measurement of the diameter of the FO at its maximal angle to the attachment point as defined by previous studies, with a redundant aneurysmal septum primum bulging [?]50% into the left atrium and flattening the septum, and with a FO flap swinging at less than 30° into the left atrium[6,7]. The inner diameters of the ascending aorta and main pulmonary artery were measured at systole in the long-axis sagittal view when the great arteries were in parallel orientation. Pulse Doppler was used to measure the flow rates of the great arteries and to assess the direction of blood flow in the DA. In terms of the constriction of the DA, we measured A peak systolic velocity in the DA of greater than 1.4 m/s was considered to be in favor of constriction[8]. Color Doppler was used to detect VSDs and measure its diameter both in the four-chamber view and when visualizing the outlets of the great arteries in the sagittal section of the heart. All echocardiographic measurements and quantitative findings were recorded.

2.4 Postpartum management of neonates with d-TGA

We recommended delivery after as late as 39 weeks of gestational age in the absence of a restrictive FO and an IVS. After delivery, all neonates underwent neonatal echocardiography to confirm the diagnosis of d-TGA. All neonates confirmed having d-TGA were admitted to the NICU and received PGE infusions until surgery. Postpartum parameters included gestational age at birth, birth weight, umbilical cord pH, Apgar's scores at 1 and 5 minutes, oxygen saturation by pulse oximetry (sPO_2), need for respiratory support, duration of PGE infusions, and the need for urgent BAS within 48 hours of delivery indicated by inadequate blood mixing at the atrial level and a sPO_2 of less than 75% despite PGE infusions as well as the day of an arterial switch operation. A BAS performed within 48 hours of delivery was considered to be urgent [9].

2.5 Statistical analysis

Data were processed using the Statistical Package for the Social Sciences 28 (SPSS) program. Categorical data are presented as numbers and frequency, continuous data as means with standard deviation or as medians with interquartile range (IQR). The Kolmogorov-Smirnov test was used to test the normality of distribution of variables. Categorical data were compared using the chi-squared test or Fischer's exact test, and continuous data using the Student's t-test or Mann-Whitney U-test. Receiver operating characteristic (ROC) analysis was performed to determine cut-off values for the diameters of FO and VSD to predict urgent BAS. After univariate analysis with possible factors thought to be associated with urgent BAS, variables that were significantly related to urgent BAS in univariate analysis and other factors that may be associated with urgent BAS were included in the multivariate analysis. Hosmer–Lemeshow goodness of fit statistics was used to assess model fit. A P value of less than 0.05 was considered significant.

3 RESULTS

During the study period, 64 fetuses were diagnosed with d-TGA, which was also confirmed postnatally. Of these, 16 fetuses were excluded due to additional cardiac anomalies or the inability to reach the mother. In total, 48 cases were included in this series (Figure 1).

Twenty-nine percent of the neonates were female. The mean maternal age was 30.5±6.0 years. Cesarean section was performed in 37 (77%) cases because of prenatal detection of restrictive appearance of the FO in 5 cases, obstetric reasons in 25 cases and maternal request in 7 cases. The median gestational age at delivery was 39 weeks (IQR 1) week. Maternal clinical characteristics are presented in Table 1.

Prenatal genetic testing was performed in 12 fetuses, which showed no karyotype anomalies or 22q11 microdeletion.

3.1 Fetal echocardiographic findings

Table 2 presents fetal cardiac assessments made at a median of 38 gestational weeks. Ventricular septal defect was found in 41.7% of the fetuses, most commonly of membranous subpulmonary type (50%). There was no ventricular disproportion or high-velocity flow in both the great arteries and DA, confirming the absence of constricted DA. The mean diameter of the FO was 5.9±1.2 mm. Restrictive FO was present in 5 fetuses (10.4%).

3.2 Neonatal outcomes

Neonatal outcomes are summarized in Table 3. Eighteen neonates (37.5%) required urgent BAS, immediately after birth (n=13, 27.1%), on the first day after delivery (n=4, 8.3%) and on the second day after delivery (n=1, 2.1%).

On prenatal echocardiography, only 3 of 13 fetuses requiring urgent BAS immediately after birth had VSD. In these 13 fetuses, the median FO diameter was 5.1 mm (IQR 1.6). Of four fetuses requiring urgent BAS on the first day of life, only one had VSD. In these 4 fetuses, the median FO diameter was 5.1 mm (IQR 0.4). The remaining fetus that required urgent BAS on the second day of life had an IVS with a median FO

diameter of 5.4 mm (IQR 0). All 5 fetuses with a restrictive FO appearance and an IVS underwent urgent BAS immediately after birth. In these fetuses, the median FO diameter was 4.1 mm (IQR 0.3).

Non-urgent BAS was performed in 5 neonates (10.4%) beyond 48 hours of life due to postnatal echocardiographic detection of left ventricular outflow tract obstruction (subvalvular pulmonary stenosis). The median time to non-urgent BAS was 15 days (IQR 6). All the fetuses undergoing non-urgent BAS had VSD, with a median FO diameter of 6.3 (IQR 3.2) mm. None underwent arterial switch operation. One neonate underwent Rastelli operation at 11 months, another underwent Nicaidoh operation at 15 months, and another underwent Glenn operation at 24 months. The remaining two newborns were under follow-up.

In total, 43 neonates underwent arterial switch operation, 18 of whom required urgent BAS. The median FO diameter was 5.1 mm (IQR 1.6) in the urgent BAS group as compared with 6.3 mm (IQR 1.3) in fetuses without urgent BAS.

3.3 Association of urgent BAS with prenatal IVS, VSD and FO

Within this cohort, 28 fetuses (58.3%) had d-TGA with an IVS, and 20 (41.7%) had d-TGA with a VSD. Among the former group, 14 neonates (50%) underwent urgent BAS while 14 (50%) did not, whereas among the latter group, 4 (20%) underwent urgent BAS while 16 (80%) did not. There was a significant association between IVS and urgent BAS*(p=.03)* (Table 4). The median VSD diameter of the fetuses undergoing urgent BAS was 2.5 mm (IQR 0.25), as compared with 3.85 mm (IQR 1.23) in fetuses without urgent BAS (p=.05).

Overall, the median FO diameter was 6 mm (IQR 1.53). The median FO diameters were 6.4 mm (IQR 1.5) and 5.9 mm (IQR 1.4) in those with and without VSD, respectively (p=.08).

The median FO diameter was significantly decreased in fetuses who required urgent BAS, as compared with those without urgent BAS (5.1 mm vs 6.3 mm, p=.002).

Neonates undergoing urgent BAS differed significantly from those without urgent BAS with respect to APGAR 1 min, basal pH, basal O_2 saturation, duration of PGE infusions, FO diameter, and the presence of restrictive appearance of FO and VSD (p<.05) (Table 5).

3.4 Receiver operating characteristic analysis for the diameters of the FO and VSD for urgent BAS

Receiver operating characteristic curve analysis showed a good discriminatory estimate of FO and VSD diameters in predicting urgent BAS in patients with d-TGA. A cut off of 6 mm for the FO diameter (sensitivity, 73.3%; specificity, 72.2%; area under the curve [AUC], 0.764) and 3.2 mm for the VSD diameter (sensitivity, 75%; specificity, 75%; AUC, 0.728) suggested urgent BAS (Table 6) (Figure 2).

3.5 Fetal predictors of urgent BAS

We evaluated potential fetal predictor factors for urgent BAS for neonates with d-TGA. The results of multivariate logistic regression analysis of are presented in Table 7. The FO diameter and the presence of VSD were independent variables associated with urgent BAS in fetuses with d-TGA (p<.05).

3.6 Complications, follow-up results and mortality

There was no termination of pregnancy or intrauterine death, but two neonates who had switch operation on the second postnatal day died of sepsis each on the 12^{th} and 14^{th}postoperative days. The mortality rate was 4.1%.

4 DISCUSSION

In fetuses with d-TGA, severe hypoxemia may occur in the neonatal period due to inadequate blood mixing at the atrial level in the absence of VSD, making early detection and follow-up essential in experienced centers. In our study population, the FO diameter and the absence of a VSD were predictors of urgent BAS in fetuses with d-TGA.

According to definitions by Rudolph et al., [10,11] in fetuses with d-TGA with an IVS, cardiovascular circulation is characterized by blood reaching the left atrium via the FO and the left ventricle carriers oxygenated blood to the pulmonary circulation and then to the descending aorta. This condition results in restriction of the DA and increased pulmonary venous return to the left atrium, which may be associated with narrowing and restriction of the FO owing to the elevated pressure in the left atrium [12-14]. In our study, the FO diameter was significantly decreased in the urgent BAS group, compared with the fetuses without urgent BAS (5.1 mm vs 6.3 mm). This finding is consistent with a report of 45 fetuses with d-TGA and IVS, in which the median FO diameter was significantly decreased (5.7 mm), requiring urgent BAS [15]. Our study group also included fetuses with both VSD and IVS. In another study, the median FO diameter was 4.8 mm in the urgent BAS group as compared with 5.9 mm in fetuses not required urgent BAS, but the differences were not significant [16].

In ROC analysis, a FO diameter of 6 mm was found to predict urgent BAS with a sensitivity of 73.3% and specificity of 72.2%. In our experience, a FO diameter of greater than 6 mm highly reduced the need for urgent BAS. Similar to our finding, in a study of 60 fetuses, the FO diameter was significantly smaller in the urgent BAS group and the FO diameter was found to be the most valuable predictor for urgent BAS, though their cut off value on the ROC analysis was greater (6.5 mm). This difference may arise from the incidences of VSD, being 41.7% in the current study vs 18% in their study group[17]. Besides FO, some authors also used the ratio of FO to the total septal length (FO:TCL), with a FO:TCL of 0.5 yielding a higher predictive value for urgent BAS with a sensitivity of 99%, specificity of 60%, positive predictive value of 50% and negative predictive value of 94%[18].

In our study, 5 fetuses had restrictive appearance of FO and no high-flow rate in the DA, suggestive of absence of constriction of the DA. While one fetus had an aneurysmatic FO with its flap extending more than 50% to the left atrium, the remaining four had a flat FO flap swinging less than 30° into the left atrium. In accordance with other studies, all 5 fetuses underwent urgent BAS immediately after birth[16,18]. There are also some studies suggesting that the appearance of the FO flap (flat, fixed or aneurysmatic) was not associated with urgent BAS [19-22]. Inconsistencies between studies may result from the small number of fetuses included, the definition of urgent BAS, the lack of echocardiographic examination after 37 weeks of gestation, or misdiagnosis of FO restriction in normal fetuses due to breathing movements and physiological right ventricular hypertropia. In addition, interpretation of the FO may vary due to the primary or secondary nature of restriction: the former represents an abnormally narrowed aneurysmatic FO and motility, while the latter may result from hemodynamic alterations including abnormal blood flow in the DA and pulmonary venous return [23]. In our study, in 13 fetuses requiring urgent BAS, narrowing of the FO was possibly caused by underlying d-TGA hemodynamics, i.e., the pumping of blood with high oxygen saturation directly from the left ventricle to the lungs, causing increased pulmonary venous return to the left atrium.

In our experience, the presence of a VSD appeared to play a protective role from urgent BAS: only 4 of 20 fetuses with VSD underwent urgent BAS. In a retrospective single center study, BAS was performed in 64% of neonates with an IVS and 25% of neonates with VSD[24]. In addition to the FO diameter, the absence of VSD was found to be an independent predictor of urgent BAS (Table 7). In the ROC analysis, the cut off value for the VSD diameter was 3.2 mm, with 75% sensitivity and 75% specificity.

BAS can generally be thought of as a safe procedure. In our study, no complications developed in the neonates who underwent urgent BAS. In a study of 73 neonates undergoing BAS, the procedural success rate was 98.6%, while hemodynamically significant arrhythmia developed in 4.1%, tamponade in 1.4%, and catheter-related complications in 2.7%[24].

The strengths of this study are the comprehensive analysis of the FO and VSDs with echocardiographic examinations performed most commonly after 37 weeks of gestation and a single center study. There are two limitations to this study. First, its retrospective design. Second, we could not include the FO in ROC and regression analyses in fetuses with VSD or IVS separately due to the small number of the fetuses.

In conclusion, prenatal echocardiography performed after 37 weeks of gestation in fetuses with d-TGA

provides valuable information about the dimensions of FO and the absence of VSD to estimate the need for postnatal urgent BAS that would prevent immediate life-threatening complications.

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FIGURE 1. Distribution of the included and excluded patients, d-TGA dextro-transposition of the great arteries.

Abbreviations: BAS, balloon atrial septostomy; PS, pulmonary stenosis; TA, tricuspid atresia; DILV, double inlet left ventricle; LSVC, left-sided superior vena cava; AoC, aortic coarctation.

FIGURE 2. Receiver operating characteristics curve for FO and VSD diameter in predicting to urgent BAS.

Abbreviations: FO, foramen ovale; VSD, ventricular septal defect; BAS, balloon atrial septostomy.

TABLE 1. Maternal clinical and demographical characteristics (n=48)

Parameters	**Number or median**
Maternal age, year	31 (7)
Maternal parity	1 (1)
Cesarean section	37 (77%)
Consanguinity	6 (12.5%)
Maternal comorbidities	
Pregestational diabetes	1 (2.1%)
Gestational diabetes	14 (29.2%)
Hypothyroidism	6 (12.5%)
Family history of CHDs	0

Data are presented as median (IQR) or n (%).

Abbreviations: CHD, congenital heart disease.

TABLE 2. Fetal cardiac features

Fetal cardiac assessment	
Gestational age at scan, weeks	38 (1)
VSD	20 (41.7%)
VSD diameter, mm	3.6 (1.5)
VSD type Muscular Inlet Membraneous subpulmonary	6 (30%) 4 (20%) 10 (50%)
Foramen ovale diameter, mm	6.0 (1.5)
Restrictive appearance of the foramen ovale	5 (10.4%)
Restricted ductus arteriosus	0
Ventricular disproportion	0
Main pulmonary artery diameter, mm	9.3 (2.6)
Main ascending aorta diameter, mm	7.7 (1.7)

Data are presented as median (IQR) or n (%).

Abbreviations: VSD, ventricular septal defect.

TABLE 3. Neonatal features

Neonatal assessment	
Neonatal gender, female	14 (29.2%)
Birth weight, gr	3148 (420)
GA at delivery, weeks	39 (1)
APGAR 1. Min	6.57 (1)
APGAR 5. Min	7.8 (0.1)
Neonatal CPR	5 (10.4%)
Neonatal entübation	6 (13.8%)
Preoperative O2 saturation	80 (8.25)
Preoperative pH	7.27 (0.09)
Neonatal PGE infüsion	48 (100%)
Duration of PGE infüsion, day	3 (4.25)
Urgent BAS	18 (37.5%)
İmmediately after delivery	13 (72.0%)
First day after birth	4 (22%)
Second day after birth	1 (5%)
Non-urgent BAS	5 (10.4%)
The day of non-urgent BAS, day	15 (6)
Arterial switch operation	43 (89.6%)
The day of arterial switch operation, day	4 (2)
Duration of hospitalization, day	17 (4)
Mortality	2 (5%)

Data are presented as median (IQR) or n (%).

Abbreviations: GA, gestational age; CPR, cardiopulmonary resuscitation; PGE, prostaglandin E; BAS, balloon atrial septostomy.

TABLE 4. Ballon atrial septostomy according to VSD

	VSD	**VSD**	
	Present (n=20)	Absent (n=28)	p

	VSD	**VSD**	
Urgent ballon atrial septostomy			
Yes (n=18)	4 (20%)	14 (50%)	**.03**
No (n=30)	16 (80%)	14 (50%)	
Non-urgent ballon atrial septostomy			
Yes (n=5)	5 (25%)	0	**.005**
No (n=43)	15 (75%)	28 (100%)	
Patients with urgent and non-urgent BAS			
Yes (n=23)	9 (45%)	14 (50%)	.732
No (n=25)	11 (55%)	14 (50%)	

Data are presented as n (%).

Abbreviations: VSD, ventricular septal defect; BAS, balloon atrial septostomy.

TABLE 5. Fetal and neonatal outcomes according to urgent BAS

	Urgent BAS	**Urgent BAS**	p
	Yes (n=18)	No (n=30)	
Maternal age, year	31 (10.5)	31 (5.5)	.798
Gender, female	7 (38.9%)	7 (23.3%)	.177
Birth weight, gr	3148 (248)	3148 (480)	.77
Gestational age, week	39 (1)	39 (1)	.367
Gestational diabetes mellitus	5 (27.8%)	9 (30%)	.87
The present of maternal comorbidity	8 (44.4%)	13 (43.3%)	.94
APGAR 1 min	6.57 (0.42)	6.57 (0.89)	**.041**
APGAR 5 min	7.95 (0.1)	7.89 (0.77)	.202
Neonatal entübation	0	6 (20%)	.072
Basal pH	7.19 (0.09)	7.30 (0.07)	**.001**
Basal 0_2 saturation	70 (8.25)	85 (7.75)	**.001**
Duration of PGE infüsions, day	1 (0)	4 (2.75)	**.001**
Length of hospitalisation, day	16.5 (4.5)	17 (3.95)	.765
Foramen ovale diameter, mm	5.1 (1.52)	6.3 (1.33)	**.002**
Restrictive appearance of the foramen ovale	5 (27.8%)	0%	**.005**
Ventricular septal defect	4 (22.2%)	16 (53.3%)	**.034**

Data are presented as median (IQR) or n (%).

TABLE 6 . Foraman ovale and VSD diameter cut-off values for urgent balloon atrial septostomy

	AUC	Cut-off points	Sensitivity	Specificity	PPV	NPV
Foraman ovale	0.764	6	73.3%	72.2%	81.48%	61.9%
VSD diameter	0.828	3.2	75%	75%	92.3%	42.8%

Abbreviations: AUC, area under the curve; VSD, ventricular septal defect.

TABLE 7. Logistic regression analysis for factors associated with not to require urgent balloon atrial septostomy

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	B	*SE*	*p*	*OR*	*Lower*	*Upper*
Maternal age	-0.119	0.071	.095	0.888	0.772	1.021
Gestational DM	-1.544	1.065	.147	0.214	0.026	1.722
The presence of VSD	2.127	0.987	**.031**	8.390	1.212	58.093
FO diameter	1.191	0.426	**.005**	3.291	1.427	7.589

Nagelkerke R Square 0.416, Hosmer and Lemeshow Test Sig 0.906.

Abbreviations: DM, diabetes mellitus; VSD, ventricular septal defect; FO, foraman ovale.

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