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Increased Nuchal Translucency and Pregnancy Outcomes: A Tertiary Center Data

Artmış Nukal Translusensi ve Gebelik Sonuçları: Bir Üçüncü Basamak Merkez Verileri

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ABSTRACT

Aim: This study aimed to evaluate the pregnancy outcomes of patients who applied to our clinic between the 11th and 14th weeks of pregnancy and whose nuchal translucency (NT) measurement was ≥1.5 multiples of the median (MoM).
Material and Methods: The study included 85 patients whose NT measurement was determined ≥1.5 MoM and pregnancy results were available. Demographic characteristics of the patients, prenatal invasive diagnostic test results, fetal anomaly screening, fetal echocardiography (ECHO) results, and neonatal and obstetric results were evaluated.
Results: Abnormal karyotype was detected in 10.6% (n=9) of the patients. Trisomy 21 was the most common chromosomal anomaly. Fetal structural anomaly was detected in 29.4% (n=25) of the patients. A structural fetal anomaly was detected in 21% (n=13) of fetuses with normal karyotypes and 66.7% (n=6) of fetuses with abnormal karyotypes. Cardiac anomalies were found to be the most common anomalies with 9.7% (n=6) in patients with normal karyotype. NT and NT MoM values in patients with fetal structural (both p=0.001) or chromosomal anomalies (p=0.011, and p=0.019, respectively) were found significantly higher than those without. NT and NT MoM values in patients whose pregnancies resulted in fetal loss were found significantly higher than in patients who had a live birth (both p=0.001).
Conclusion: Increasing NT or NT MoM values indicate an increase in the risk of chromosomal anomalies, structural anomalies, and poor pregnancy outcomes in the fetus. Fetal anomaly screening and fetal ECHO should be recommended in patients with increased NT, even if a normal karyotype is detected.
Keywords: Abnormal karyotype; anomaly; increased nuchal translucency.

ÖZ

Amaç: Bu çalışmanın amacı, gebeliğin 11. ile 14. haftaları arasında kliniğimize başvuran ve nukal translusensi (NT) ölçümleri ortancanın ≥1,5 katı (multiples of the median, MoM) olan hastaların gebelik sonuçlarını değerlendirmektir.
Gereç ve Yöntemler: Çalışmaya NT ölçümü ≥1,5 MoM olarak tespit edilen ve gebelik sonuçlarına ulaşılabilen 85 hasta dahil edildi. Hastaların demografik özellikleri, prenatal invaziv tanı testi sonuçları, fetal anomali taraması, fetal ekokardiyografi (EKO) sonuçları ile neonatal ve obstetrik sonuçları değerlendirildi.
Bulgular: Hastaların %10,6 (n=9)'sında anormal karyotip saptandı. Trizomi 21 en sık görülen kromozom anomalisiydi. Hastaların %29,4 (n=25)'ünde fetal yapısal anomali tespit edildi. Normal karyotipli fetusların %21 (n=13)'inde ve anormal karyotipli fetusların %66,7 (n=6)'sinde yapısal fetal anomali tespit edildi. Kardiyak anomaliler normal karyotipli hastalarda %9,7 (n=6) ile en sık görülen anomali olarak bulundu. NT ve NT MoM değerleri, fetal yapısal (her iki p=0,001) veya kromozomal anomalisi olan hastalarda (sırasıyla p=0,011 ve p=0,019) olmayanlara göre anlamlı olarak daha yüksek bulundu. Gebeliği fetal kayıp ile sonuçlanan hastalarda NT ve NT MoM değerleri, canlı doğum yapan hastalara göre anlamlı olarak daha yüksek bulundu (her iki p=0.001).
Sonuç: NT veya NT MoM değerlerinin artması fetusta kromozomal anomaliler, yapısal anomaliler görülme riskinin ve olumsuz gebelik sonuçlarının artmasına işaret eder. NT artışı olan hastalarda normal karyotip tespit edilse bile fetal anomali taraması ve fetal EKO önerilmelidir.
Anahtar kelimeler: Anormal karyotip; anomali; artmış nukal translusensi.

INTRODUCTION

Detecting fetal anomalies in the early stages of pregnancy is one of the most important purposes of prenatal sonography. Nuchal translucency (NT) occurs due to fluid accumulation in the subcutaneous tissue at the back of the fetal neck and can be evaluated by ultrasonography (USG) between the 10^{th} and 14^{th} weeks of pregnancy. NT measurement is the most important part of the first trimester combined screening test for aneuploidy screening (1). By combining NT measurement with maternal serum markers PAPP-A and free β-hCG, Down syndrome detection rates reach 80-90% (2-4).

Increased NT is defined as the measured NT value being ≥95^{th} percentile or ≥1.5 multiples of the median (MoM) according to the fetal crown-rump length (CRL) (5). In addition to leading to the detection of chromosomal diseases, NT increase is also associated with poor pregnancy outcomes such as many genetic syndromes, fetal structural anomalies, and fetal loss (6-11).

In this study, it was aimed to evaluate the prenatal and postnatal outcomes of pregnant women who applied to our clinic between the 11^{th} and 14^{th} weeks of gestation and whose NT measurement was ≥1.5 MoM.

MATERIAL AND METHODS

Approval for the study was received from the local ethics committee of Van Yüzüncü Yıl University (approval date: 18.11.2022 and number: 11-27). The outpatient records and electronic hospital information system of 18,505 patients who applied to Van Yüzüncü Yıl University Faculty of Medicine Perinatology clinic between 2018 and 2022 were retrospectively scanned. Patients with NT measurement ≥95^{th} percentile between the 11^{th} and 14^{th} weeks of gestation were included in the study. CRL and NT measurements were performed in accordance with the measurement criteria determined by the Fetal Medicine Foundation (FMF) (12). NT measurements were converted to MoM values according to CRL with FMF's NT calculation programs. 105 patients with increased NT measurements were identified. However, 20 patients were excluded from the study because their pregnancy results could not be obtained. All patients were evaluated at the perinatology council and families were given detailed information about the prognosis. For prenatal diagnosis, patients were offered the option of invasive diagnostic tests, chorionic villus sampling, and amniocentesis. Quantitative fluorescent polymerase chain reaction (QF-PCR) and cytogenetic culture were requested from all patients who had an invasive diagnostic test, according to the recommendations of the genetics department. Fetal anomaly screening was performed between the 18^{th} and 22^{nd} weeks of gestation. Voluson E6 model (General Electric Healthcare, USA) 2-5 MHz transabdominal probe was used for NT evaluation and fetal anomaly screening. By scanning the digital hospital data system, the demographic characteristics of the patients, prenatal karyotype results if performed, fetal anomaly screening, and fetal ECHO results were found. By scanning the hospital data system, the pregnancy results of the patients who continued their pregnancy follow-up in our hospital were obtained. All patients included in the study were contacted via their registered telephone information and asked how the pregnancy ended (spontaneous abortion, intrauterine fetal death, termination, live birth) and whether any abnormalities (mental, motor development, organ-system dysfunction) were detected during the postnatal neonatal examination and the postnatal follow-up of the child.

Statistical Analysis

Shapiro-Wilk test, and skewness and kurtosis values were used to check whether the continuous measurements in the study were normally distributed. Parametric tests were applied for normally distributed variables. Descriptive statistics were expressed as mean±standard deviation, median, interquartile range, minimum-maximum, number of patients, and percentage. Independent samples t-test was used to compare measurements between the groups. The statistical significance level was taken as $p<0.05$, and the IBM SPSS (IBM SPSS for Windows, ver.26) statistical package program was used for analyses.

RESULTS

In the present study, 18,505 patient data were examined retrospectively. 105 (0.6%) patients with NT measurement ≥95^{th} percentile according to CRL were identified. However, 20 patients were excluded from the study because their pregnancy results could not be obtained.

The median age of patients was 29 (range, 19-45) years, the median number of gravida was 2 (range, 1-12), parity was 1 (range, 0-5), abortions was 0 (range, 0-6), living children was 1 (range, 0-5), the median gestational week was 12^{+4} (range, 11^{+0}-14^{+2}) in the form of week^{+day}. The median CRL was 56 (range, 41-83) mm, the median NT was 3.8 (range, 3.0-7.9) mm and the median NT MoM was 2.6 (range, 1.6-6.4). Demographic and ultrasonographic characteristics of the patients were shown in Table 1.

Of the patients, 31.8% (n=27) wanted to have a prenatal invasive diagnostic test for karyotype analysis, and chorionic villus sampling was performed in 10 patients, and amniocentesis was performed in 17 patients. A chromosomal anomaly was found in 29.6% (n=8) of the patients who had invasive diagnostic testing. While 62.5% (n=5) of the chromosomal anomalies were Trisomy 21, 25% (n=2) were Trisomy 18, and 12.5% (n=1) were 45XO. Fetal ECHO was performed in 30.6% (n=26) of the patients. Fetal cardiac anomaly was detected in 34.6% (n=9) of the patients who underwent fetal ECHO. Fetal anomaly screening was performed in 75.3% (n=64) of the patients.

Table 1. Demographic and ultrasonographic characteristics of the patients

	Median	IQR	Min-Max
Age (years)	29	25-34	19-45
Gravida	2	2-4	1-12
Parity	1	0.5-2	0-5
Abortion	0	0-1	0-6
Living child	1	0.5-2	0-5
Pregnancy week	12^{+4}	12^{+0}-13^{+4}	11^{+0}-14^{+2}
CRL (mm)	56	52-70	41-83
NT (mm)	3.8	3.2-4.8	3.0-7.9
NT MoM	2.6	2.1-3.6	1.6-6.4

CRL: crown-rump length, NT: nuchal translucency, MoM: multiples of the median, mm: millimeter, IQR: interquartile range (25^{th}-75^{th} percentile)

Congenital fetal anomaly was detected in 29.7% (n=19) of the patients who underwent fetal anomaly screening. 74.1% (n=63) of the patients' pregnancies resulted in live births, 11.8% (n=10) in intrauterine fetal death, 5.9% (n=5) in spontaneous abortion, and 8.2% (n=7) in termination. During the examination and follow-up of the newborn after live birth, normal findings were detected in 79.3% (n=50), and abnormal findings were found in 15.9% (n=10). Three babies died after live birth. Prenatal and postnatal results of the patients were shown in Table 2.

When prenatal and postnatal results were evaluated together, the chromosomal anomaly was found in 10.6% (n=9) of the patients. Fetal karyotype could not be determined in 16.5% (n=14) of the patients. Fetal karyotypes could not be determined in 11 patients because their pregnancies resulted in fetal loss without invasive diagnostic testing after the detection of NT increase, and in three patients with neonatal death after live birth, they did not have karyotype analysis in both the prenatal and postnatal periods. Normal karyotype was detected in 72.9% (n=62) of the patients, while fetal anomaly was detected in 29.4% (n=25). A structural fetal anomaly was detected in 21% (n=13) of the fetuses with normal karyotypes, 66.7% (n=6) of fetuses with abnormal karyotypes, and 42.9% (n=6) of fetuses with unknown karyotypes. While the live birth rate was found to be 76.9% (n=10) in fetuses with normal karyotypes with anomalies, this rate was found to be 98% (n=48) in those without anomalies. The results of the patients according to their chromosomal anomaly status were shown in Table 3.

Of the patients with prenatal fetal structural anomaly, 47.3% (n=9) had cardiac anomaly and 26.3% (n=5) had hydrops fetalis. Central nervous system anomaly was detected in four patients, facial anomaly in two patients, kidney anomaly in two patients, anterior abdominal wall defect in two patients, and extremity defect in two patients. 47.3% (n=9) of the anomalies were multiple anomalies. When prenatal and postnatal results were evaluated together, the most common anomalies were cardiac anomalies at 9.7% (n=6) and facial anomalies at 4.8% (n=3) in patients with normal karyotypes. Among the patients with abnormal karyotype detected prenatally, only the pregnancy of the patient whose result was 45XO resulted in live birth, while the pregnancy of four patients was terminated upon their request and the pregnancies of three patients resulted in intrauterine fetal death. The characteristics and pregnancy outcomes of patients with karyotype and/or fetal anomalies were shown in Table 4.

During the examination and follow-up of the newborn after live birth, abnormal findings were detected in 20.6% (n=13) of the babies. New findings were detected in the postnatal period in seven of the patients who did not have prenatal invasive diagnostic testing and fetal anomaly screening. During the newborn examination and follow-up after live birth, cleft lip in two babies, cleft palate and undescended testicle in one baby, ventricular septal defect (VSD) and aortic coarctation in one baby, VSD in one baby, Trisomy 21 in one baby, and growth retardation in one baby were detected during follow-up. Anomalies detected in the newborn examination and follow-up after live birth in patients who did not have a prenatal diagnostic test and fetal anomaly screening were shown in Table 5.

NT measurements and NT MoM values of patients with abnormal karyotypes were found to be significantly higher than those of patients with normal karyotypes (p=0.011, and p=0.019, respectively). NT measurements and NT MoM values of patients with fetal structural anomaly were found to be significantly higher than those of patients without fetal structural anomaly (both p=0.001). NT measurements and NT MoM values of patients whose pregnancies resulted in fetal loss were significantly higher than those of patients who had a live birth (both p=0.001). During the examination and follow-up of the newborn after live birth, NT measurements and NT MoM values of patients with pathological findings were found to be significantly higher than those of patients with normal findings (both p=0.001). The comparison of prenatal and postnatal results in terms of NT and NT MoM values was shown in Table 6.

Table 2. Prenatal and postnatal outcomes of the patients

	n (%)
Invasive diagnostic testing	
Normal karyotype	19 (22.4)
Abnormal karyotype	8 (9.4)
Did not do	58 (68.2)
Fetal echocardiography	
Normal	17 (20.0)
Anomaly detected	9 (10.6)
Did not do	59 (69.4)
Fetal anomaly screening	
Normal	45 (52.9)
Anomaly detected	19 (22.4)
Did not do	21 (24.7)
Pregnancy outcome	
Live birth	63 (74.1)
Intrauterine fetal death	10 (11.8)
Spontaneous abortion	5 (5.9)
Termination	7 (8.2)
Status of the newborn after live birth	
Normal	50 (79.3)
Abnormal	10 (15.9)
Ex	3 (4.8)

Table 3. Results of patients according to chromosomal anomaly status

	Karyotype						
	Normal (n=62)		**Abnormal (n=9)**			**Unknown (n=14)**	
	Anomaly (+) (n=13, 21.0%)	**Anomaly (-) (n=49, 79.0%)**	**Anomaly (+) (n=6, 66.7%)**	**Anomaly (-) (n=2, 22.2%)**	**Unknown (n=1, 11.1%)**	**Anomaly (+) (n=6, 42.9%)**	**Unknown (n=8, 57.1%)**
Live birth	10 (76.9)	48 (98.0)	0 (0.0)	2 (100)	0 (0.0)	3 (50.0)	0 (0.0)
Intrauterine ex	0 (0.0)	1 (2.0)	3 (50.0)	0 (0.0)	0 (0.0)	2 (33.3)	4 (50.0)
Abortion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	4 (50.0)
Termination	3 (23.1)	0 (0.0)	3 (50.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)

Table 4. Characteristics and pregnancy outcomes of patients with karyotype and/or fetal structural anomalies

NT (mm)	NT MoM	Karyotype result	Fetal anomaly scan result	Pregnancy result
6.6	3.8	Did not do	Omphalocele + hypoplastic left heart	IU fetal death
5.2	3.6	Trisomy 21	AVSD + spina bifida	IU fetal death
4.4	3.2	Normal	Aortic stenosis	Live birth
4.5	4.2	Did not do	VSD	Live birth
6.8	5.1	Trisomy 21	Hydrops fetalis	IU fetal death
7.7	4.3	Trisomy 21	Did not do	Termination
4.8	3.8	Normal	Hydrocephalus	Termination
5.6	5.3	Trisomy 18	Hydrops fetalis	IU fetal death
4.8	3.4	Did not do	VSD + aortic coarctation + multicystic kidneys	Live birth newborn ex
4.8	3.5	Normal	Hypoplastic left heart	Termination
4.2	3.2	Trisomy 18	Diaphragmatic hernia + bilateral club foot + hydrops fetalis	Termination
4.9	3.4	Did not do	Pleural effusion + micrognathia + hypotelorism	Live birth newborn ex
7.0	5.3	Normal	Omphalocele + multicystic kidney	IU fetal death
7.0	3.8	Normal	Dandy walker variant + diaphragmatic hernia + bilateral club foot	Termination
7.0	5.3	Did not do	Hydrops fetalis	IU fetal death
3.8	3.3	Did not do	Micrognotia + cerebellar hypoplasia + nasal hypoplasia	Live birth newborn ex
7.5	6.4	Did not do	Truncus arteriosus	Spontaneous abortion
4.0	2.9	45XO	No anomalies	Live birth
4.8	2.9	Did not do	VSD	Live birth
6.2	3.2	Trisomy 21	AVSD + nasal hypoplasia	Termination
5.4	4.1	Trisomy 21	Hydrops fetalis	Termination

NT: nuchal translucency, MoM: multiples of the median, AVSD: atrioventricular septal defect, VSD: ventricular septal defect, IU: intrauterine

Table 5. Anomalies detected in newborn examination and follow-up after live birth in patients not had prenatal invasive diagnostic testing and fetal anomaly screening

Anomaly	Number of patients
Cleft palate + undescended testicle	1
Cleft lip	2
Growth failure	1
VSD + Aortic coarctation	1
VSD	1
Trisomy 21	1

VSD: ventricular septal defect

Table 6. Comparison of NT and NT MoM values in terms of prenatal and postnatal results

	Karyotype		p
	Normal	Abnormal	
NT (mm)	4.21±1.23	5.65±1.25	**0.011**
NT MoM	2.86±1.10	3.96±0.90	**0.019**

	Fetal anomaly screening		p
	Normal	Abnormal	
NT (mm)	3.43±0.50	5.46±1.16	**0.001**
NT MoM	2.28±0.64	3.91±0.93	**0.001**

	Pregnancy result		p
	Live birth	Fetal loss	
NT (mm)	3.68±0.66	5.76±1.26	**0.001**
NT MoM	2.46±0.69	4.20±0.86	**0.001**

	Status of the newborn		p
	Normal	Abnormal	
NT (mm)	3.47±0.48	4.51±0.59	**0.001**
NT MoM	2.24±0.49	3.30±0.68	**0.001**

NT: nuchal translucency, MoM: multiples of the median

DISCUSSION

While NT increase allows the detection of chromosomal anomalies, especially Down syndrome, in the prenatal period, it is also associated with poor pregnancy outcomes such as many genetic syndromes, fetal structural anomalies, and fetal loss (6-11). Increased NT is seen in 0.5% to 1.75% of pregnant women in the general population (13,14). During the period when the study was conducted in our clinic, this rate was found to be 0.6% (n=105). Although we are a busy clinic, the reason why we found a rate close to the lower limit stated in the literature is that the majority of patients come to our clinic between the ages of 18-22. We thought it was because they applied for fetal anomaly screening during the gestational weeks.

In our study, only 31.8% (n=27) of the patients had invasive diagnostic testing. When prenatal and postnatal results are evaluated together; Chromosome anomalies were detected in 10.6% of the patients, most commonly Trisomy 21 and Trisomy 18. It has been reported in the literature that chromosomal anomalies are detected in 20% to 44% of the patients with increased NT (9,15-16). In a large study by Kagan et al. (17), evaluating 11,315 patients with increased NT, the chromosomal anomaly was found in 19% of the patients. In a study by Boutot et al. (18), evaluating 398 patients, invasive diagnostic testing was performed in 87% of the patients, and chromosomal

anomalies were detected in 37.4% of the patients, the most common being Trisomy 21. In another study in which a similar chromosomal anomaly rate was detected as our study, invasive diagnostic testing was performed on 50% of the patients, and a 12.1% rate of chromosomal anomaly was detected, the most common being Trisomy 21 (19). We thought that the majority of patients did not undergo invasive diagnostic testing due to the socio-cultural structure and religious beliefs of our region. In our study, karyotype analysis could not be performed on 16.6% (n=14) of the patients. We thought that the 14 patients for whom karyotype analysis could not be performed affected the chromosomal anomaly detection rate and that if karyotype analysis could be performed on these patients, we could detect a higher chromosomal anomaly rate. We could not identify a specific syndrome in our study. However, due to multiple anomalies, fetal loss was encountered. We thought that it might be among the patients who died. Additionally, only conventional karyotyping is performed in our hospital. Chromosomal microarray analysis (CMA) and other advanced genetic tests were not studied. In a meta-analysis in which fetuses with increased NT and normal karyotypes were evaluated, the chromosomal anomaly detection rate of CMA was found to be 5% (20). If CMA could have been studied in our study, more chromosomal anomalies could have been detected.

Increased NT is also associated with poor pregnancy outcomes such as fetal structural anomaly and loss (6-11). In our study, prenatal and postnatal results were evaluated together and fetal structural anomaly, most commonly cardiac anomaly, was detected in 29.4% (n=25) of the patients. Structural anomalies, most commonly cardiac and then facial anomalies, were detected in 21% (n=13) of patients with normal karyotypes. In a study in China where 264 patients with increased NT were evaluated, fetal anomalies were detected in 22.3% of the patients, the most common being hydrops, followed by cardiac anomalies (19). Senat et al. (15) detected structural anomalies in 27% of patients with increased NT. Boutot et al. (18) detected structural anomalies in 28.7% of the patients, the most common being cardiac and then urogenital anomalies. In another study, structural anomaly was detected in 9% of 834 cases with increased NT and normal karyotype (11). In our study, it was observed that the 21% (n=13) fetal structural anomaly rate detected in patients with normal karyotypes increased to 29.4% (n=25) with the addition of patients with abnormal karyotypes or unknown karyotypes. It was thought that this was due to fetal structural anomalies that often accompany chromosomal anomalies. Our fetal anomaly detection rates were found to be compatible with the literature.

In our study, 74.1% (n=63) of the patients' pregnancies ended in live births and 25.9% (n=22) in fetal loss. It was found that pregnancy loss was 23.1% (n=3) in patients with normal karyotype if accompanied by fetal structural anomaly, and 2% (n=1) if not accompanied by fetal structural anomaly. In a study, fetal loss rates of up to 13% were reported in patients with increased NT, especially if they were accompanied by structural anomalies (21). In another study evaluating pregnant women with normal karyotype and increased NT, fetal loss was found to be 7.14% (22). In another study evaluating pregnant women with normal karyotype and increased NT, total fetal loss was found to be 15.8%. In the same study, the fetal loss rate was found to be 58.3% in the group with fetal structural anomaly and 3.5% in the group without fetal structural anomaly (23). In our study, consistent with the literature, it was observed that poor pregnancy outcomes became evident when the presence of structural anomalies was added to the increase in NT.

In our study, NT and NT MoM values were found to be significantly higher in patients with fetal anomaly than in patients without fetal anomaly, and in patients with abnormal karyotype compared to patients with normal karyotype. NT and NT MoM values were found to be significantly higher in patients with fetal loss or abnormal newborn examination compared to the patients without. Similar to our study, Uysal et al. (23) found NT and NT MoM values to be significantly higher in the group with an increase in NT and a fetal anomaly or pregnancy loss compared to the group without a fetal anomaly or pregnancy loss (23). In another study evaluating the pregnancy outcomes of increased NT, it was found that 73% of fetuses with normal karyotypes were in the group with the lowest NT value (11). In a study in which 720 patients with increased NT and normal karyotype were evaluated, significant results were found indicating that as the NT value increased, the risk of fetal anomaly, cardiac anomaly, hydrops fetalis, abortion, and intrauterine fetal death increased (24). Our findings support that, similar to other studies in the literature, poor pregnancy outcomes increase as NT and NT MoM values increase.

CONCLUSION

NT evaluation is very important in antenatal follow-up. In our study, as in other studies in the literature, NT increase is associated with chromosomal anomalies, fetal structural anomalies, and poor pregnancy outcomes. We observed that as NT or NT MoM values increased, the risk of chromosomal anomaly, structural anomaly, and poor pregnancy outcomes in the fetus increased. It was found that detecting fetal anomalies in patients with normal karyotypes increased poor pregnancy outcomes. Increased NT increases the risk of fetal anomalies. For these reasons, fetal anomaly screening and fetal ECHO should be recommended in patients with increased NT, even if a normal karyotype is detected.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Van Yüzüncü Yıl University (18.11.2022, 11-27).

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