

Can nuchal cord be responsible for later neurodevelopmental disorders?

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Abstract: To established the link between the umbilical cord wrapped around the neck (nuchal cord- NC) and the neurodevelopmental (ND) outcome of the child. We studied 275 newborns over the eight-year period, - one group of 160 newborns with one or multiple NC loops (study group), and another group of 115 newborns with no NC (control group). Newborns examined in this study are from normal course of pregnancies and deliveries and both genders. Both groups of newborns were monitored through pediatric clinic, whereby the assessment of their neurodevelopmental outcome over the one year period was conducted using the Munich Functional Developmental Diagnosis (MFDD protocol). Based on MFDD protocol, there was statistically significant ND deviation in the study group comparing to the control group. ND outcome at the age of 1 year is associated with pathological CTG (fetal heart rate) results. Statistically significant influence was observed in tightened umbilical cord wrapped around the neck (tCAN - tight cord around the neck) on the ND outcome at the age of 1 year. There was significant correlation between t-CAN and ND outcome. Our study has shown that higher tCAN phase is resulting in greater ND deviation ($p < 0.001$). Control group with no tCAN had normal ND outcome in 95.65 % of cases. Good prenatal NC diagnostic, using doppler and color ultrasound as well as cardiotocography, is important in assessment of severity of clinical picture of newborn and deciding about the delivery methode.

Keywords- nuchal cord , tCAN, newborns, neurodevelopmental outcome, prenatal diagnostic,color Doppler, cardiotocography

1 INTRODUCTION

Having in mind historical facts, interest for nuchal cord (NC) on fetus and its connection to perinatal mortality and morbidity, exist since the time of Hypocrite. [1]. NC definition refers to situation where the umbilical cord is strangled around fetus' neck by 360 degrees. Its first official description occurred in year 1962. [2]. NC finding is often at the delivery with different incidence, from 6 - 29 % and even more in some studies, depending on gestational age [3,4,5,6]. Although it is not usual to expect increased perinatal mortality or morbidity, NC is mentioned as the risk factor at perinatal mortality and morbidity with consequent late neurodevelopmental disorders . [5,6,7,8,9]. Researches gone through some studies have brought controversial results. Pathophysiological moments that occur due to compression of the umbilical cord wrapped around the neck of the fetus can cause obstruction and reduction of blood flow, resulting in hypovolemia, acidosis and anemia, and may be associated with later developmental disorders [5,10,11]. The aim of our study was to link the presence of umbilical cord wrapped around the neck of the fetus at birth, to neurodevelopment of child until the age of 1 year.

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2.1. SUBJECT

The research was clinical-prospective, conducted during the period from 2005. to 2013. Included were pregnant women from Una Sana Canton, on whose children, NC (single or multiple loops around the neck) was

2 SUBJECT AND RESEARCH METHODS

diagnosed. Subjects (study group) were 160 newborns with single or multiple loops around the neck, born in Sanski Most general hospital and Bihać cantonal clinic „Dr Irfan Ljubijankić“, during the period from 2005. to 2013. Included children were born at term and are of both genders. Control group consisted of 115 newborns with no NC and from regular pregnancies.

Criteria for inclusion: newborns from regular, in-term pregnancies, in which at birth the NC with single or multiple loops around the neck was diagnosed, without associated anomalies, with spontaneous delivery or caesaeran.

Criteria for exclusion: preeclampsia, intraamniotic infection,HELLP syndrome, premature birth, pregnancy induced hypertension, diabetes mellitus and other anomalies.

2.2. METHOD

The NC diagnosis is set by gynecologist according to Crawford definition [2]. Prenatal information about pregnancy, the course of pregnancy, childbirth course (fetal heart rate and amniotic fluid) and the delivery itself (whether natural or caesaeran) were obtained from the gynecological protocol of General Hospital Sanski Most and Cantonal Hospital "Dr. Irfan Ljubijankić" in Bihać. Neonatal anthropometric measurements, gestational age at birth, APGAR score and perinatal outcome were entered into neonatal sheet.

Demographic, socioeconomic and medical parameters are inserted into special questionnaires, with the permission of parents. Socio-economic index is taken as the consensus of the US office, professional qualification and employment status. However, we neither processed nor compared this data during this study. We have analysed the fetal heart rate, which has been marked as regular or pathological, and then the APGAR score with infants grouped into three groups: from 1-4, from 5-7 and from 8-up. From 1-4 was defined as heavy asphyxia, from 5-7 as slight asphyxia, and 8 and up as no asphyxia. Depending on number of nuchal cord loops around the neck we divided all the subjects into two groups: group I with 1-2 loops, and group II with 3 or more loops around the neck. Based on clinical symptomatology according to Preesau, we graded the nuchal cord (NC) tenseness as: Gr 0 - where there was no clinical symptomatology, Gr I - those who had conjunctival hemorrhage

and petechiae, Gr II - those with facial cyanosis, face suffusion and pallor, and Gr III - respiratory distress, stupor and hypotonia.

All children from both groups, with the NC and as well without, were monitored through the pediatric clinic whereby the evaluation of psychomotor development is conducted according to the Munich functional developmental diagnostics (MFE) [12]. The examinations were conducted at the age of 1, 3, 6, 9 and 12 months. Evaluations for each chronological age were entered into a special forms/records.

According to MFE, following has been evaluated: development of motor skills, activities such as crawling, sitting and walking, fine and gross motor skills-catching, sensibly perceptual functions, speech and understanding of speech as well as socialization, all according to the prescribed chronological age of development (MFE Diagram at the age of 1 year attached). Additional tests were done in cases where required in order to diagnose possible hearing or eyesight discrepancy.

At the end of the first year of life, we have characterized the psychomotor development as regular if all the criteria were defined as satisfied for prescribed age, as slightly deviating in case of any deviation from one area of development, and as derogation if there were two or more criteria which differing from prescribed age.

Statistics

In this study, methods of table- and graphic presentation have been used, as well as Chi-square test and correlation. Connection between the psychomotor status and monitored health status factors is shown through graphics.

Dependence between the factors is tested by Chi-square test in case of non-numeric variables (health status), and/or Kendall correlation coefficient where variables expressed in grades. Empirical p value < 0.05 indicates that there is a statistically significant relationship.

For statistical analysis of the data obtained software system SPSS for Windows (version 13.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excel (version 11 Microsoft Corporation, Redmond, WA, USA) will be used.

3 RESULTS

The study group consisted of 160 infants, born at term, with NC with single or multiple loops around the neck, born in two hospitals in Una-Sana Canton. The control group consisted of 115 infants without NC, as well born at term. The study group consisted of 110 males (68.75%) and 50 females (31.25%) .

Incidence of umbilical cord around the neck with respect to the total number of births was in this period 29.01%.

Analyzing the fetal heart rate deceleration in a group of children with the NC, it is statistically significant incidence of pathological fetal heart rate (in 56,25% of cases) in the study compared to the control group (in 16.52% of cases). (p<0.001)

Tabel 1. Fetal heart rate

	Group A		Group B		Total
pathological	90	56.25 %	19	16.52%	109
Normal	70	43.75%	96	83.48%	166

Group A: study group with NC .
Group B: control group without NC.

In the study group there was statistically significant higher incidence of completing of delivery with cesarean section, as well as comparing to the control group. (p<0,001.)

Vaginal/natural delivery is more typical for the control group (group B).

Tabel 2. Mode of delivery

	Group A	Group B	Total
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Natural	103	64,38 %	97	84,35 %	200	100
Sectio cesarea	57	35,63 %	18	15,65 %	75	100
Total	160	100,0 %	115	100,0 %	275	

Group A: study group with NC .
Group B: control group without NC.

Analyzing fetal heart rate deceleration in relation to the mode of delivery in both groups, we observe the correlation between the groups; and, the most vaginal/natural deliveries have had normal fetal heart rate (68.00%), while pathological fetal heart rate was in most of the caesarean sections (60,00 %).

Tabel 3. Mode of delivery in study group - Group A

	Group A - I (1 and 2)		Group A-II (3 and 3+)		Total
Vaginal/normal delivery	93	58,12%	10	6,25%	103 64,37%
Sectio cesarea	51	31,87%	6	3,75%	57 35,62%
Total	144	90,00%	16	10,00%	160 100,00%

Group A- I: infants with one or two umbilical cord loops around the neck (1 and 2).
Group A-II:infants with three of more umbilical cord loops around the neck (3 and 3+)

Analyzing the number of umbilical cord loops and mode of delivery, we have not found any statistically significant correlation between the two groups (A-I with one and two umbilical cord loops and group A-II with three and more loops). (x²=0,027, p=0,869)

Tabel 4. APGAR score

APGAR score	Group A	Group B	Total
1-4	12 - 7.50%	0 – 0,00 %	12
5-7	32 - 20.00%	4 - 3.48 %	36
8 +	116 - 72.50%	111 - 96.52 %	227
Total	160 -100,00 %	115 –100.00 %	275

Group A: study group with NC .
Group B: control group without NC.

Analyzing the APGAR score in test group with NC comparing to the control group, we have proved statistical significance of lower APGAR score in study group (p< 0,001).

Tabel 5. APGAR score in study group - Group A

APGAR score	Group A - I	Group A - II	Total	p-
1-4	7 - 4.37%	5 - 3,12%	12	7,50%

					%	15,00%	3,75%	0.00%	0.00%	18,75%
5-7	27 - 16,87%	5 - 3,12%	32	20,00%	3	10	1	0	1	12
					%	6,25%	0,625%	0.00%	0,625%	7,5%
8 <+	110 - 68,75%	6 - 3,75%	116	72,50%	Total	55	102	2	1	160
						34,37%	63,75%	1,25%	0,625%	100%
Total	144 -90,00%	16 -10,00%	160	100,00%						

Group A- I: infants with one or two umbilical cord loops around the neck (1 and 2).
Groupa A-II:infants with three of more umbilical cord loops around the neck (3 and 3+)

Comparing the number of umbilical cord loops and APGAR score, we have realised statistically significant correlation between the above two, i.e. increasment of number of umbilical cord loops is followed by lower APGAR score (p< 0,001).

On the basis of Munich functional diagnostics it has been shown that there was a statistically significant deviation in the study group compared to the control group (p< 0,001).

Table 6. PMD 1 - psychomotor development at the age of 1 year in booth group

	Group A-I	Group A-II	Group B	Total
PMD deviation	45	10	1	56
PMD regular	96	6	110	212
PMD minimal deviation	2	0	4	6
Total	143	16	115	274

PMD 1 - psychomotor development at the age of 1 year
Group A- I: infants with one or two umbilical cord loops around the neck (1 and 2).
Groupa A-II:infants with three of more umbilical cord loops around the neck (3 and 3+)
Group B: control group without NC.

During the process, one child deceased while two children have shown minimal deviation; however, this could not been included into statistical analysis due to the inability of comparison (the number/percentage is too low for statistics).

Chi-square test has been used to test the dependance between t-CAN and PMD. However, although patients with minimal deviation (two patients), and exitus (1 patient) have had lower fetal heart rate frequencies, they have been excluded from the analysis.

Based on Chi-square test value of 59.58 it is to be concluded that there is statistically significant correlation between tCAN and PMD whereby the more complex tCAN has as a results heavier deviations (empirical p value of the test <0.001).

Table 7. The influence of tight cord around the neck (tCAN) on PMD 1

tCAN	Study group				Total
	PMD 1 - with deviation	PMD 1 - regular	PMD 1 - minimal deviation	PMD 1 - exitus	
0	10	69	1	0	80
%	6,25%	43,125%	0,625%	0.00%	50,00%
1	11	26	1	0	38
%	6,85%	16,25%	0,625%	0.00%	23,75
2	24	6	0	0	30

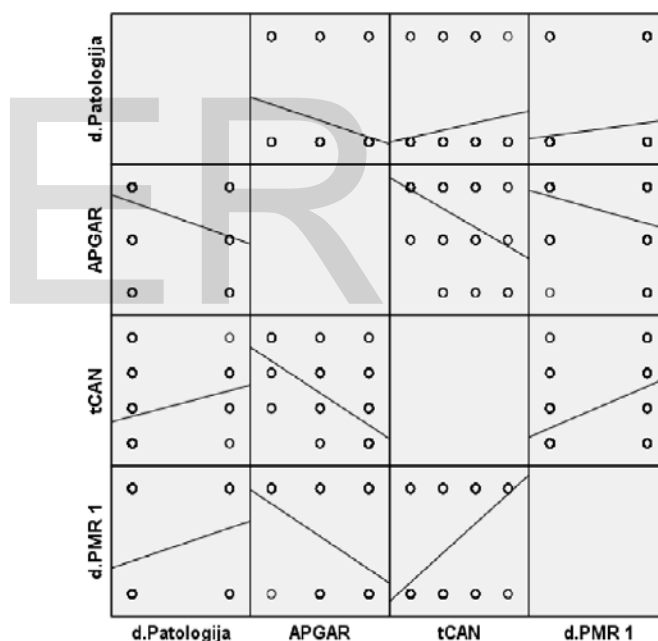
Control group has no tCAN, so PMD at the age of 1 year is regular in 95,65%.

Control group is more often negative comparing to the study group with statistical significance (p <0.001).

Table 8. PMD 1 - psychomotor development at the age of 1 year In Control group

	Number of patients	%
deviation	1	0.87
regular	110	95.65
minimal deviation	4	3.48
Total	115	100.00

Diagram among selected variables:



The direction indicates the course of correlation where a growing inclination means that the increase of the horizontal axis variable value results in increase of PMD 1.

Ascending curves indicate that the increasment is followed by deterioration of status, while desending indicate that the value increase is heading towards regular results.

Increasing number of tCAN loops increases the PMD 1 deviation. Increasing value of APGAR score reduces the possibility of PMD 1 deviations.

Table 9. Correlation – significant (Kendall's tau b)

			d.PMD at 1 year	d.Patolog y	APGAR	tCAN
Kendall's tau b	d.PMD 1	Correlation Coefficient	1,000	,197*	-,419**	,567**
		Sig. (2-tailed)	.	,013	,000	,000
		N	275	160	275	275
	d.Patolog y	Correlation Coefficient	,197*	1,000	-,280**	,234**
		Sig. (2-tailed)	,013	.	,000	,002
		N	160	160	160	160
	APGAR	Correlation Coefficient	-,419**	-,280**	1,000	,545**
		Sig. (2-tailed)	,000	,000	.	,000
		N	275	160	275	275
	tCAN	Correlation Coefficient	,567**	,234**	-,545**	1,000
		Sig. (2-tailed)	,000	,002	,000	.
		N	275	160	275	275
*. Correlation is significant at the 0.05 level (2-tailed).						
**. Correlation is significant at the 0.01 level (2-tailed).						

4 DISCUSSIONS

The incidence of umbilical cord around the neck (nuchal cord - NC) of the fetus during the period of study was 29.01% compared to the number of deliveries in both hospitals. Taking into account the incidence with respect to the number of deliveries, the greater number of infants with NC were born at term. We conducted our study on 160 children with NC at birth. All the deliveries in our study were at term, between 37 and 42 gestation weeks (GW). Similar results describes as well Larson where there was 6% of infants from 20 weeks of gestation and 29% of 42 gestational weeks. Several scientific researches describe the increasing NC incidence with increasing gestational age [9,13,14,22,29,32]. Large retrospective study describes the frequency of NCA 6.6% to 21.6%. [6] Comparison of low gestational age to infants born in term, in relation to NC, was not possible since the infants from lower gestational age were not included into our study. Out of the 160 children there were 68.75% male infants which is significantly higher representation of male children with NC in relation to female children. Other studies also proved increased number of male children with NC [3,10,15,16,44]. APGAR score was more often lower in children with NC (3,5,10,16,22,24,25,40). Birth weight was lower in group with NC [7,27]. Several studies also confirm similar results. It is considered that chronic intermittent umbilical cord compression may lead through hypoxia to fetal intrauterine growth retardation (16,28). NC is associated with an increase of lower APGAR score. It is to be noted that sometimes the APGAR score is not an indicator of fetus asphyxia. A much better indicator is the umbilical cord blood pH; although tight umbilical cord around the neck (tCAN) and incidence of lower APGAR score can, as the risk factor, increase the incidence of fetal distress syndrome and presence of meconium stained amniotic fluid. For the occurrence of fetal hypoxia it is observed significant difference between the study group and multiple nuchal loop as well as between the study group with 1 nuchal cord loop and with 2 or more nuchal cord loops (39). In our study, sectio cesarea (SC) is statistically more often used for the completion of delivery in the group with NC - 35, 63%, while vaginal delivery in the control group - 15.65% (p <0.001). Considering other studies, there are different results and opinions regarding the completion of delivery with elective CS. Schaefer et al did not describe the increased number of Caesarean sections in the NC group (3,24,28,30); Gupta et al did not confirm the increase of cesarean section deliveries in cases with umbilical cord around the neck [30].

About the statistical significance of Faethal heard rate (FTH) deceleration (and meconium staining of liquor were statistically higher) in newborns with NC indicate in their papers and Khusboo and some other authors. [6,21, 40, 41,42]

Some authors describe even controversial results, increased frequency of SC delivery even in the group without NC [5,25,32]. Joshi K. is quoting same increment of SC in NC group but without statistical significance [21,23,26]. Similar results were presented by Miser but also with no statistical significance [15]. We can explain this by better monitoring during the delivery whereby the SC is to be conducted only where required, based on monitoring parameters, while elective SC is not advocated. It has been noted that there is an indication for SC in an emergency cases and it is important to use the gynecological ultrasound in order to estimate the best moment for the caesarean section.

Analyzing the risk factors in children with CAN, APGAR scores, higher degree of NC tanglement and higher number of loops around the neck, have statistically significant correlation with PMD deviation. Due to the compression respectively obstruction of blood vessels in the umbilical cord in the group with NC, hypovolemia and anemia as well hypotension may arise, which may reduce cerebral blood flow through the brain which consequently may lead to neurodevelopmental damage. Cord compression, whether chronic, acute or intermittent, leads to centralization of blood flow protecting vital organs (heart, brain and adrenal glands). Fetal response to hypoxia development is the release of catecholamines, cortisol and vasopressin and angiotensin and other biochemical substances. Glucose and gluconeogenesis metabolism is disrupted which leads to increased lactate which further leads to acidosis. This can later result in bradycardia, vasodilatation, fetal hypotension and heavier acidosis. Consequently it comes to fetal decompensation with cardiac failure, arrhythmia, or fetal death [38]. Some studies suggest that those fetuses that have managed to establish a compensation although having clinical symptoms, NC with lower Apgar score was not always responsible for the later psychomotor deviation, while abnormal fetal heart rate and multiple loops may cause neurodevelopmental disorders and unexplained spastic cerebral palsy [31]. Group of authors who examined the connection between asphyxia, as a risk factor, and cerebral palsy, have found no connection between the NC and the CP. [34,36] Experiments on animals with NC have proven changes which are responsible for the disruption in the development of oligodendrocytes and myelin disruption, resulting in changes in gray and white matter [35]. Study of Clapp et al., where the children with NC were tested at the end of first year of life using Bayley Scale, found a statistical significance between the children with NC and the control group whereby the NC group had deviation in neurodevelopment. In our study we did not recorded any cases of CP which is logical because the diagnosis of CP is not to be diagnosed before the age of 3 and our study was covering the period until the age of 1 year.

NC is described as one of the risk factors for the development of autism [34]. Early symptoms of autistic spectrum (AS) were not diagnosed as autistic spectrum disorder but were entered into our forms for assessing the overall development and will continue to be monitored.

Number of loops around the neck is associated with developmental disorders at the end of the first year of life. Similar results were described as well by other authors [8].

In our study, the psychomotor development was statistically significant deviating with regard to the control group. It is significant that the deviation have been recorded with an increased incidence in the group with the 3 or more NC loops and with symptomatology graded by grade 3. One child deceased, 2 children had minimal PMD development deviation, out of which 1 was from the group without symptomatology, and 1 from the group with grade 2, however none of the above were counted into the statistical analysis due to low number.

Our study is limited to the assessment of psychomotor development with the child's first year of life, whereby Munich functional developmental diagnostics used, which includes all the important parameters for assessing one year of development. Two children with minimal deviation on the above criteria are not covered by statistical analysis. The lack of this study is the short-term monitoring.

5 CONCLUSION

1. High incidence of NC at birth, which as well other authors describe.
2. Pathological fetal heart rate with the completion of delivery by caesarean section.
3. The presence of higher number of loops / higher CAN results in lower APGAR score.
4. Lower APGAR score, number of NC loops and grade of clinical symptomatology - grade 3, have statistically significant impact on PMD assessed by the Munich functional early diagnostics.[44]
5. Systematic gynecological ultrasound monitoring along with prenatal diagnostic of the number of NC loops and monitoring of antropometric values and heart rate action will help us to determine in which manner the delivery is to be completed. [6,43]
6. Our study is limited since showing a short-term results of the PMD assessment. We find necessary to continue systematic long-term monitoring in order to reach adequate results and relate them to possible NC complications.
7. The importance of quality of antenatal care.

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