Neonatal Abstinence Syndrome – Diagnostic Dilemmas in the Maternity Ward

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SUMMARY

Introduction Neonatal abstinence syndrome (NAS) refers to a newborn neurological, gastrointestinal and/or respiratory disorder if a newborn was exposed to psychoactive substances in the intrauterine period. NAS is difficult to diagnose due to unreliability of the data on addictive substances use during pregnancy, limited possibilities of the prenatal exposure diagnosis and postnatal substance detection, which all lead to diagnostic dilemmas.

Objective The aim of this study was to indicate the problems in patients with early NAS diagnosis in the maternity ward and the importance of clinical presentation used as a guide toward the diagnosis.

Methods This retrospective study included five term eutrophic newborns with high Apgar score, good adaptation in the first day and with clinical presentation of NAS during the second day of life. The clinical presentation was dominated by irritability, increased wakefulness, increased muscle tone, shrilly crying, tremors, problems with accepting food, tachypnea, subfebrility and hyperhidrosis. Finnegan scale was introduced in order to diagnose NAS and apply the therapy. Single-medication therapy of phenobarbitone was applied in four cases and a combination of phenobarbitone and morphine in one case. For toxicological analysis newborns' urine samples were used.

Results Conditions such as perinatal asphyxia, infection, hunger, polycythemia, hypoglycemia or hypocalcemia were excluded. Finnegan score implied that pharmacological treatment had to be administered. The discrepancy between the NAS anamnesis and toxicological analysis existed. Response to the treatment was positive in all cases.

Conclusion NAS is a multisystemic disorder and should be suspected when it is noticed that children exhibit characteristic signs. However, other pathological conditions have to be excluded. Quantification according to the adopted scales for NAS leads toward appropriate treatment and recovery of the newborns.

Keywords: newborn; neonatal abstinence syndrome; substances of misuse

INTRODUCTION

Neonatal abstinence syndrome (NAS) refers to a newborn neurological, gastrointestinal and/or respiratory disorder if a newborn was exposed to psychoactive substances in the intrauterine period. The substance inflow is lost after the birth and elimination commences, which is the base for newborn's abstinence syndrome clinical manifestation – the deprivation mechanism [1].

Regardless of the primary cause, NAS is characterized by similar symptoms. NAS is most commonly caused by addictive substances such as opiates, cocaine, marihuana, amphetamine, alcohol, nicotine, as well as by numerous medicines – barbiturates, benzodiazepines, antidepressants, etc., which are used during pregnancy in medical purposes, as well as by their misuse during pregnancy. The type of addictive substance, dosage, period of exposition, the last exposition as well as newborn's metabolism and excretion of stool are the main factors which affect when clinical presentation of NAS occurs and how serious it is. Clinical presentation usually manifests in the course of the first 48–72 hours of the child's life, early NAS, or during the second or third week, late NAS – methadone NAS [1, 2].

The NAS incidence is difficult to determine due to unreliability of the data on addictive substances use during pregnancy, limited possibilities of the newborn prenatal exposure diagnosis and postnatal substance detection. Therefore, the base for the prompt diagnosis is a high level of suspicion [3, 4, 5].

NAS is increasingly becoming more and more pertinent for modern neonatal practice, which is proportionate to the increase of percent of people using psychoactive substances. One quarter of narcotic users are women in their fertile period of life [3, 5].

Without employing the standard method of NAS assessment, clinicians have been making notably different decisions regarding the NAS monitoring and treatment. Finnegan score (FS) was introduced in 1973. It was modified in 1975 and since then it was used as a predictive score for the clinical evaluation and as a guideline for the NAS pharmacological treatment. Various pharmaceuticals have been used for the newborn abstinence syndrome treatment. Main drugs used for NAS treatment are phenobarbitone and morphine, which are orally administered [1, 3, 6-9].

Urine, meconium, blood, hair and nails are used for the NAS toxicological diagnosis [2, 3, 8, 10].

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OBJECTIVE

The aim of this study is to present our experiences with diagnosis and therapy of NAS in the maternity ward through the cases of five newborns with NAS, with special regard to the importance of respecting the main doctrine in medicine – clinical presentation used as a guide toward the diagnosis.

METHODS

This retrospective study included five cases of NAS. The clinical presentation was in different degrees dominated by neurological change (hyperalert state – increased wakefulness, short periods of sleep, irritability, shrilly crying, increased tone, tremors, spontaneous Moro reflex), gastrointestinal symptomatology (problems with accepting food with prominent sucking reflex), short respiratory (moments of tachypnea) and vegetative disorder (subfebrility, hyperhidrosis). In all cases other pathological conditions were excluded: perinatal asphyxia (high Apgar score, good adaptability during the first day of life, normal gas analysis, normal central nervous system ultrasound), infection (good vaginal and cervical smears of the mothers, newborns' complete blood count and C-reactive protein within reference ranges, normal hemoculture), metabolic imbalance (normal electrolyte status, normoglycemia), polycythemia (normal hemoglobin and hematocrit levels), hunger (minimal body mass loss, between 2.3% and 3.4%, rejection of additional feeding and drinking).

More extensive anamnesis included interview of the mothers about narcotic, medication, alcohol and nicotine misuse. Heteroanamnesis included spouses and mothers' parents. Medical charts of the mothers were reviewed as well.

Evaluation of significant neurological, respiratory, gastrointestinal, vegetative signs according to the adopted Finnegan scale was commenced in order to diagnose and quantify NAS. Finnegan scale enables semiquantitative evaluation of clinical presentation of NAS by scoring 16 clinical symptoms and signs (crying, reflexes, muscle tone, sleep, tremors, generalized convulsions, body temperature, sweating, yawning, sneezing, respiratory rate, sucking, feeding, regurgitation, vomiting, type of stool). If symptoms do not disappear with conservative measures such as holding, swaddling, frequent feeding, isolation, minimal stimulation and intravenous crystalloids, and the value of three successive FS are equal or higher than eight in a two- to four-hour interval, pharmacological therapy is necessary. FS is used for increasing or decreasing of pharmacological therapy and was determined in three-hour intervals.

The newborns were treated in the intensive neonatal care unit. All the newborns were treated with non-pharmacological treatment and with mono-therapy which included phenobarbitone. The newborn treated with double-therapy (phenobarbitone and morphine) was sent to the intensive neonatal care unit of an institution of the tertiary level. Controlled serum dosages of phenobarbitone were within the allowed limits (20–40 mg/l) throughout the course of the treatment and they were reduced upon the termination of the treatment application.

For toxicological analysis, the newborns' urine samples were used. The samples were taken during the second day of the life before applying the pharmacological treatment, and then sent to the laboratory of referent institution – Military Medical Academy. Toxicological screening was done with semiquantitative analysis of drugs and their metabolites as well as with immunochromatographic assay. Substances which can be detected by these analyses are the following: benzodiazepines, phenothiazine, antidepressants, cardiotropic drugs, opiates, cannabis, amphetamines, cocaine and ecstasy.

RESULTS

Five cases of eutrophic term newborns with high Apgar score and good adaptation during the first day of life are reported in this study. At the beginning of the second day of life, a change in the general state of the newborns occurred and clinical presentation of NAS was manifested. The pregnancies of mothers were regularly checked. The vaginal and cervical smears of the mothers were normal. The delivery terminated in natural childbirth in case of two patients and in a Caesarean section in other three (Table 1).

Mothers' anamneses were negative in three cases, while in the third case the mother had been a former heroin addict, on the substitution methadone treatment for the previous three years (80 mg/day for the previous six months). In the fourth case the mother had been a former heroin addict as well, on the substitution methadone treatment for the previous six months (20 mg/day). Additionally, mother of the fifth newborn reported misuse of heroin in the early gestation, and use of methadone drops in the late gestation. Heteroanamnesis was negative in each case, except in the third, where the father was a former heroin addict. FS varied from eight to 17 in four cases and in one case was up to 23. The newborns' toxicological urine analyses were positive in two cases (Table 2).

Table 1. Delivery data of the neonates

Delivery data	Case				
	I	II	III	IV	V
Type of delivery	Vaginal delivery	Caesarian section	Vaginal delivery	Caesarian section	Caesarian section
Gestational age (weeks)	38.4	39.2	41.1	39.6	41
Neonatal body weight (g)	3,000	3,080	3,400	2,900	3,550
Apgar score 1st and 5th min	9/10	9/9	8/9	9/9	9/9

doi: 10.2298/SARH1510573L

Table 2. Clinical characteristics and symptoms of the neonates

Characteristics	Case				
	I	II	III	IV	V
Mother's anamnesis	Negative	Negative	Positive	Positive	Negative
Heteroanamnesis	Negative	Negative	Positive	Negative	Negative
Urine analysis	Negative	Positive	Negative	Negative	Positive
Finnegan score	11–13	17–23	11–17	9–13	11–14

Table 3. Therapy and response to the therapy

Therapy	Case				
	I	II	III	IV	V
Non-pharmacological treatment*	Applied	Applied	Applied	Applied	Applied
Single-therapy	Phenobarbitone (8 mg/kg/day)	Phenobarbitone (12 mg/kg/day)	Phenobarbitone (12 mg/kg/day)	Phenobarbitone (6 mg/kg/day)	Phenobarbitone (10 mg/kg/day)
Double-therapy	Not applied	Morphine	Not applied	Not applied	Not applied
Response to the treatment	Positive	Positive	Positive	Positive	Positive

* intravenous crystalloid solution

Non-pharmacological treatment was applied in every case, as well as phenobarbitone (daily dosage 6–12 mg/kg). Controlled serum dosages of phenobarbitone were within the allowed limits throughout the course of the treatment and were reduced (13.11 mg/l) upon the termination of the treatment application. Morphine was added to the therapy only in the second case, where the FS was the highest (maximum daily dosages recommended for the NAS treatment). The pharmacological treatment of the reported newborns lasted from four to 30 days. Response to the treatment was positive in all five cases (Table 3).

DISCUSSION

According to literature, NAS clinical presentation is stated to vary and a newborn with this syndrome has nonspecific symptoms. The most common signs are irritability, high anxiety, weak and uncontrolled sucking, persistent shrilly (shrieky) crying. Moments when the newborn ceases to cry may occur, however it happens very rarely. When newborns exhibit these signs, it is important to suspect NAS [3, 9].

It is evident that the symptomatology occurred toward the end of the first and the beginning of the second day of life in the reported clinical presentations of our newborns. After the umbilical cord had been cut, the inflow of the substance was stopped, while all newborns had good diuresis and regular meconium discharge. Everything led to addictive substance elimination, which caused the abstinence syndrome onset [1]. Early NAS was suspected.

It is not easy to confirm diagnosis of NAS. Mother interview method can notably underestimate the true significance of misuse. The anamnestic psychoactive substances misuse data are unreliable due to negating or minimization [3, 4, 11]. The five newborns reported illustrate that in three newborns with the manifested NAS clinical presentation we had negative mother's anamnesis and negative heteroanamnesis. Moreover, the parents' negation of psychoactive substances misuse is evident even when the existence of psychoactive substances has been detected, more than once, in a newborn's urine (positive for heroin), which clearly indicates the discrepancy between the NAS anamnesis and toxicology. We did not encounter negation of the previous misuse in the cases of the so-called "registered users". Communication was easily established with these mothers and precautionary measures were undertaken immediately after birth. Since methadone NAS is more likely to occur in the third week of life, the dilemma remains if there were minimizations and negations of some psychoactive substances misuse other than methadone, as a substitute medicine, in the cases of mothers with positive anamnesis. Ethanol, benzodiazepines and caffeine are known to potentate psychoactive substances effects [1, 3, 11].

Taking into consideration neurological change, vegetative disorders, respiratory distress, gastrointestinal disorders, it is the obligation of a neonatologist in the maternity ward to exclude other pathological conditions as potential causes of this change prior to or in the course of the commenced scoring and treatment of abstinence syndrome.

FS has been utilized as a standard scoring system in our maternity ward for clinical monitoring, NAS quantification and as a guideline for the approach (a shrinkage or increase of dosage) of the commenced pharmacological treatment [3, 4, 12].

The decision to start pharmacological treatment was made after the scores had remained higher than eight in three-hour intervals, even with the application of non-pharmacological measures. Any pharmaceutical can be classified as a medicine modifying a disease or a medicine modifying symptoms. Phenobarbitone, medicine which modifies the symptoms, was applied. The NAS quantification showed that the score of four newborns was up to 17, with oscillations at the time of symptoms manifestation, which was used as a guideline for pharmacological treatment with one medicine. The newborns' response to the treatment was positive. The symptoms receded in the reversed order of the order of appearance: primarily vegetative and respiratory, then gastrointestinal and neurological. The most persistent was the neurological change with the predominance of hypertonia and tremor. As they recovered, the children were released from the hospital on the seventh, 13th and 15th day of life, which clearly speaks of

the syndrome seriousness and the prolonged hospitalization of this group of patients in the maternity ward [3, 13].

In the case of the newborn with FS of 17–23, double pharmacological treatment of morphine and phenobarbitone was introduced. The treatment lasted for one month in an institution of the tertiary level.

Controlled serum dosages of phenobarbitone were within the allowed limits throughout the course of the treatment and were reduced upon the termination of the treatment application. Since the response to the phenobarbitone treatment with adequate serum dosages was positive, we reached the conclusion that the medicine pharmacokinetics was suitable. The aim of the NAS pharmacological treatment is to sedate a child and lead it toward normal pace of feeding and sleeping with as small dosages as possible, which was accomplished in the treatment of our newborns [6, 8].

Urine is the most commonly used toxicological screening method of the substances of misuse. The negative side of this test is a high incidence of falsely negative findings, between 32% and 63%, since the test indicates the exposure 48 hours prior to the delivery. Presence of many substances is difficult to prove. Meconium has the highest analytical potential, since the substances reposited from the beginning of its creation (14th gestational week) can be detected in it. The test sensitivity is high and ranges from 82% to 93%. The method is significantly more expensive and available only in large centers. Negative psychoactive substance findings in meconium also do not exclude NAS. Hair analysis means a hair shaft analysis. Due to slow rate of hair growth the close-in time exposition is irretrievable and this method is also available only in large centers [2, 3, 8, 10].

The newborns' toxicological urine analyses in the scope of psychoactive substances, detected by the laboratory of referent institution, were negative in cases of three newborns. Urine was collected the second day of life when NAS was suspected, thus the lapse of time between the addictive substance use and check was prolonged, and the chance of having negative findings in that case is much higher. Furthermore, since the newborns had good diuresis and regular stools, the elimination had already started, and since they were treated with intravenous crystalloids, there was also the rinsing effect.

Given the fact that the NAS symptoms manifest with a higher degree of certainty if less than seven days lapse between the addictive substance use and the delivery, the clinical presentation can be present while urine analysis itself can be negative, as the test sensitivity is low even with exposure two days prior to the delivery. The best pieces of evidence that a substance does not exist or that it exists in low concentrations are the already manifested abstinence symptoms [1, 3, 9]. This is just one of the cases in neonatology as well as in other branches of medicine in which negative findings do not exclude the diagnosis. The course of the disease and the response to the treatment indicate that the diagnosis was correct [3].

NAS as a multisystemic disorder requires a multidisciplinary approach with an early engagement of social services [1, 3]. The treatment and monitoring of the children with NAS, which require a stay in neonatal intensive care unit, numerous short-term consequences (sudden infant death syndrome – SIDS) and long-term repercussions (poor neurological and developmental findings), are altogether a huge clinical burden.

CONCLUSION

Since the abilities of prenatal and postnatal diagnostics are limited, clinical presentation is the gold standard which leads to the diagnosis in case of a child exposed to the intrauterine psychoactive substances inflow. Clinical signs quantification according to the accepted score leads toward the appropriate non-pharmacological and pharmacological treatment selection. Score is also used to monitor the treatment response. This approach to the treatment leads toward the recuperation of the newborns with NAS and the establishment of one of the basic rhythms that a child should have upon leaving the maternity ward – the rhythm of feeding and sleeping.

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Неонатални апстиненцијални синдром – дијагностичке дилеме у породилишту

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КРАТАК САДРЖАЈ

Увод Неонатални апстиненцијални синдром (НАС) подразумева неуролошке, гастроинтестиналне и/или респираторне поремећаје код новорођенчета уколико је интраутерусно било изложено деловању психоактивних супстанци (ПАС). Ограничене могућности пренаталне и постналне детекције ПАС и негирање њиховог коришћења у трудноћи отежавају постављање дијагнозе НАС и доводе до дијагностичких дилема.

Циљ рада Циљ рада је био да се укаже на проблеме у дијагностиковању раног НАС у породилишту и на значај клиничке слике као водича ка дијагнози.

Методе рада Ретроспективна студија је обухватила пет терминских еутрофичних новорођенчади, високог Апгар скора и добре адаптираности у првом дану, са симптомима НАС у другом дану након рођења. У клиничкој слици су доминирали: иритабилност, повишена будност, повишен тонус, тремор, врискав плач, одбијање оброка, тахипнеја, субфебрилност, презнојеност. Финеган скала је коришћена за постављање дијагнозе и увођење фармаколошке терапије НАС. Уведена је монофармакотерапија фенобарбитоном код четири новорођенчета, односно терапија фенобарбитоном и морфином код једног детета. За токсиколошку анализу коришћени су узорци мокраће новорођенчади.

Резултати Искључени су перинатална асфиксија, инфекција, глад, полицитемија, хипогликемија и хипокалцемија. Финеган скор имао је вредности за увођење фармаколошке терапије код свих болесника. Постојала је дискрепанција анамнестичких података о злоупотреби ПАС током трудноће мајки и токсиколошких анализа мокраће новорођенчади. Одговор на терапију био је позитиван.

Закључак НАС је вишесистемски поремећај. Сумња на НАС је битна код новорођенчади код које су примећени типични знаци овог поремећаја. Потребно је искључити друга патолошка стања у диференцијалној дијагнози. Квантификовање према усвојеним скалама за НАС води ка правилном избору начина лечења и опоравку новорођенчади с апстиненцијалним синдромом.

Кључне речи: новорођенче; неонатални апстиненцијални синдром; супстанце злоупотребе

Примљен • Received: 13/05/2015 **Прихваћен • Accepted:** 08/06/2015