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CONTENTS

INCIDENCE, RISK FACTORS, AND NOSOCOMIAL GERMS FOR VENTILATOR-ASSOCIATED PNEUMONIA IN CHILDREN

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Abstract

Introduction. Early diagnosis and aggressive treatment is fundamental in the management of patients with ventilator-associated pneumonia (VAP).

Aim. The aim of this study was to determine the incidence of VAP among mechanically ventilated children and to identify the main risk factors and nosocomial germs for development of VAP in a critically ill PICU population.

Material and methods. A retrospective, observational study was conducted over a period of 2 years (January 2011 – December 2012) in the Fist Pediatric Intensive Care Unit (PICU) of Emergency Hospital for Children "Louis Turcanu" Timisoara and included all mechanically ventilated children ≥ 48 hours aged 0-18 years.

Results. Of all 51 mechanically ventilated patients, who met the inclusion criteria, 43.13% developed VAP. Patients with VAP needed a greater number of days of mechanical ventilation (mean 23.59 vs. 5.68 days) and a longer duration of hospitalization (mean 42.18 vs. 20.27 days) than those without VAP. Multiple regression analysis identified 4 factors associated with VAP ($p < 0.05$): previously use of an antibiotic (t-statistics (t-stat) = 2.33, $p = 0.036$), previously use of more than one antibiotic (t-stat = 2.89, $p < 0.01$), previously use of an antifungal drug (t-stat = 2.00, $p = 0.05$), and reintubation (t-stat = 2.71, $p < 0.01$). Organisms identified by culture, involved in the etiology of VAP were: gram-negative bacteria 88.8%, fungi 6.6%, and gram-positive bacteria 4.4%.

Conclusions. The incidence of VAP was higher (43%) in our study. Children on previously use of antibiotics or antifungal drugs, or experienced reintubation, developed VAP and had a longer period of mechanical ventilation and hospitalization. Pseudomonas aeruginosa was the most common Gram-negative bacteria associated with VAP.

Keywords: mechanical ventilation, children, ventilator-associated pneumonia

Introduction

VAP is defined as nosocomial pneumonia diagnosed in patients mechanically ventilated for ≥ 48 hours with signs of a new lower respiratory tract infection (1). For a correct and quick VAP diagnosis, medical staff must have a high clinical suspicion combined with blood tests, radiographic examination, and microbiologic analysis of tracheal secretions. Despite advances in supportive care, antimicrobial therapies, mechanical ventilation, and prevention of VAP, it remains an important cause of hospital morbidity and mortality (2).

The epidemiology, associated risk factors, and outcomes of VAP are not as well documented in pediatric patients as they are in adult patients. In adults, the reported incidence of VAP worldwide ranges from 8% to 28% (2,3). The most common organisms isolated from endotracheal aspirate in adult patients who developed VAP were Pseudomonas aeruginosa, Methicillin-resistant Staphylococcus aureus, Klebsiella pneumoniae and Acinetobacter baumannii (4,5). In adults, independent risk factors for development of VAP include duration of mechanical ventilation, the presence of chronic pulmonary disease, sepsis, acute respiratory distress syndrome (ARDS), neurological disease, trauma, patient age, previous antibiotic treatment, reintubation, transport out of the Intensive Care Unit (ICU), transfusions and use of histamine-2 blockers (3,6). In addition, VAP in adults has been associated with prolonged duration of mechanical ventilation as well as increased length of ICU stay, hospital stay, hospital cost, and absolute mortality (3).

The incidence of VAP depends on the population studied, the type of ICU, local infections and resistance patterns, and the diagnostic criteria used. Knowledge of the incidence of nosocomial infections and their associated risk factors may be important to allow more effective development and use of preventive measures (7).

PICU patients not only encompass a wide range of ages different from adult ICU patients but also differ in their developmental physiology, underlying disorders, and treatment needs.

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CPIS points	0	1	2
Temperature, ^{0}C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leukocyte count, /mm^3	≥ 4.000 and ≤ 11.000	< 4.000 or > 11.000	< 4.000 or > 11.000 + band forms ≥ 500
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
PaO_2/FiO_2, mmHg	> 240 or ARDS*		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

Table 1. The Clinical Pulmonary Infection Score (CPIS)

We performed this study to determine the incidence of VAP among mechanically ventilated children and to identify the main risk factors and nosocomial germs for VAP in a critically ill PICU population.

Material and methods

A retrospective, observational study was conducted over a period of 2 years (January 2011 – December 2012) in the Fist Pediatric Intensive Care Unit (PICU) of Emergency Hospital for Children "Louis Turcanu" Timisoara and included all mechanically ventilated children ≥ 48 hours, aged 0-18 years.

The following data were collected from each patient: age, sex, admission diagnosis, concomitant chronic diseases, number of days on ventilator, hospital length of stay, outcome (discharge, transfer, death).

All potential risk factors were noted: use of medications (antibiotics, antifungal drugs, steroids, continuous inotrope or vasoactive infusions, histamine type-2 receptor blockers or proton-pump inhibitors, metoclopramide, infusions of benzodiazepines or opiates), route of mechanical ventilation (nasotracheal, orotracheal, or tracheostomy), ventilation tube characteristic (cuffed versus uncuffed tube or tracheostomy), suction system (opened or closed), procedures like need for reintubation

All episodes of VAP were evaluated. VAP was define according to the Clinical Pulmonary Infection Score (CPIS), using 6 parameters (8): body temperature, white blood cells count, volume and appearance of tracheal secretions, oxygenation (PaO2/FiO2 ratio), chest X-ray, and "blind" tracheal aspirate cultures (Table 1). A score > 6 was suggestive for VAP diagnosis. The tracheal aspirates for culture were obtained under aseptic conditions using a "blind" opened suction after detaching the ventilator's tube from the endotracheal tube. The selected germs and the antibiogram from tracheal aspirate culture were also noted.

Preterm babies, patients with congenital immunodeficiency disorders or surgical diseases were excluded from the study. A patient could be included twice when two successive episodes of VAP occurred at least 7 days apart. Patients with positive endotracheal cultures who met the study definition for VAP were considered to have VAP; those who had no clinical signs and symptoms of pulmonary infection were considered to have endotracheal colonization.

This study was approved by the Hospital institutional review board.

Statistical analysis was performed using Microsoft Excel 2007 software. Results are expressed as mean ± SD. Univariate analysis was used to compare the variables for the outcome groups of interest (patients with VAP vs. patients without VAP). Comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using Student's t test for normally distributed variables. All p values < 0.05 were considered statistically significant. Results of the multiple regression analyses are reported as t-statistics with 95% confidence intervals.

Results

Of all 56 mechanical ventilated patients, 51 met the inclusion criteria. Twenty-two (43%) of them developed VAP. Six patients had more than one episode of VAP: 4 of them developed 2 successive episodes, at least 7 days apart, one patient had 3 episodes and other patient had 4 episodes of VAP, resulting in a total of 31 episodes of VAP. Demographic data for patients with VAP and without VAP are shown in Table 2. Of the 51 patients, 37 (72.5%) were males and median age was 2.2 years (26.45 month). In both groups, there were no statistically significant differences in age (p=0.54) or gender (p=0.23). Univariate analysis of admission diagnosis and concomitant chronic diseases were also not statistically significant different between those who developed VAP and those who did not. Instead, the absence of a chronic disease was found to be significant in patients who did not developed VAP (p=0.03). The most common admission diagnosis in both groups was acute respiratory failure and the most frequent concomitant disease was chronic neurological pathology (e.g. cerebral palsy). The cause of ICU admission did not correspond to the incidence of VAP in our study.

All tubes used for intubation were cuffed (Microcuff) and all suction systems were closed, both in patients with or without VAP. We did not found any differences between the intubation route (oral, nasal, or tracheostomy) and the occurrence of VAP.

The duration of mechanical ventilation was longer among patients who developed VAP (23.59±19.03 days vs. 5.68±2.37 days, p<0.01) and also the hospital stay was longer in patients with VAP (42.18±29.83 days vs. 20.27±11.51 days, p<0.01). In this study the mortality rate of patients with VAP was 22.8%. There was no significant difference in mortality between patients with VAP and those without VAP (22.8% vs. 27.5%, p=0.69).

	Non-VAP (n=29)	VAP (n=22)	p
Age (mean ±SD) month (0-216)	30.08±52.30	21.68±44.83	0.54
Sex (n, %)			0.23
Male	23 (79.3)	14 (63.6)	
Female	6 (20.7)	8 (36.4)	
Cause of ICU admission (n, %)			
Acute respiratory failure	19 (65.5)	14 (63.6)	0.89
Neurological disease	2 (6.9)	1 (4.5)	0.72
Cardiovascular disease	3 (10.3)	1 (4.5)	0.43
Severe sepsis	3 (10.3)	5 (22.8)	0.25
Others	2 (6.9)	1 (4.5)	0.72
Concomitant diseases (n, %)			
Chronic respiratory failure	1 (3.4)	4 (18.2)	0.11
Chronic neurological disease	9 (31.0)	9 (40.9)	0.47
Chronic cardiovascular disease	2 (6.9)	1 (4.5)	0.72
Malnutrition	4 (13.8)	4 (18.2)	0.68
Without chronic diseases	13 (44.8)	4 (18.2)	*0.03*
Intubation characteristics (n, %)			
Orotracheal	21 (72.4)	12 (54.5)	0.20
Nasotracheal	6 (20.6)	8 (36.4)	0.23
Tracheostomy	2 (6.9)	2 (9.1)	0.78
Endotracheal tube type (n, %)			-
Cuffed	29 (100)	22 (100)	
Uncuffed	0 (0)	0 (0)	
Suction system (n, %)			-
Closed	29 (100)	22 (100)	
Opened	0 (0)	0 (0)	
Reintubation (n, %)	1 (3.4)	7 (31.8)	*0.01*
Ventilator days (mean ±SD)	5.68±2.37	23.59±19.03	*<0.01*
Hospital length of stay (mean ±SD)	20.27±11.51	42.18±29.83	*<0.01*
Outcome			
Discharged	20 (6.8)	15 (68.1)	0.95
Death	8 (27.5)	5 (22.8)	0.69
Transferred to another hospital	1 (3.4)	2 (9.1)	0.43
Ventilator-associated pneumonia (n, %)			
1 episode only	-	16 (72.7)	-
>1 episode	-	6 (27.3)	-

Table 2. Study Population Characteristics (n=51)

Variables	Coefficients	Standard Error	t-stat	p
Antibiotics	0.35	0.15	2.33	*0.02*
Antibiotics in association	0.58	0.20	2.89	*0.005*
Antifungal drugs	0.27	0.13	2.00	*0.05*
Reintubation	0.45	0.16	2.71	*0.009*

Table 3. Variables associated with VAP, by multiple regression analysis

Variables	Coefficients	Standard Error	t-stat	p
Transfusions	-0.20	0.18	-1.05	0.29
Immunoglobulins	-0.06	0.15	-0.39	0.69
Benzodiazepines	-0.32	0.16	-1.92	0.06
Opiates	0.15	0.14	1.03	0.30
Inotrope infusions	0.08	0.17	0.50	0.61
Steroids	0.07	0.16	0.42	0.67
Metoclopramide	-0.01	0.16	-0.10	0.91
Proton-pump inhibitors	-0.15	0.14	-1.03	0.30

Table 4. Variables not significantly associated with VAP, by multiple regression analysis

	Median	Standard Deviation (SD)
CPIS score	8.16	0.68
Body temperature, ^{0}C	38.2	0.79
Leukocyte count, x10^3/mm^3	18.43	9.24
PaO_2/FiO_2 ratio, mmHg	242.45	107.82

Table 5. Numeric variables of CPIS

Pathogen	n, %
Total	**45 (100)**
Gram-negative bacteria	**40 (88.8)**
Pseudomonas aeruginosa	26 (57.7)
Klebsiella pneumoniae	8 (17.7)
Acinetobacter baumannii	3 (6.6)
Serratia marcescens	3 (6.6)
Gram-positive bacteria	**2 (4.4)**
Staphylococcus aureus MRSA	2 (4.4)
Fungi	**3 (6.6)**
Candida ssp.	3 (6.6)
Polymicrobial	**7 (15.5)**

Table 6. Microorganisms isolated from 31 episodes of VAP

Medium VAP score, according to CPIS was 8.16 (min.= 7 and max.= 9). Means and standard deviations of numeric variables of VAP score (body temperature, leukocyte count, PaO2/FiO2 ratio) are shown in Table 5.

In our study we found that the risk factors for VAP were: previously use of one (p=0.02) or more antibiotics (p<0.01), previously use of an antifungal drug (p=0.05) and reintubation (p<0.01) (Table 3). We did not find any significant differences in the occurrence of VAP and use of transfusions, immunoglobulins, continuous infusion of benzodiazepines or opiates, inotrope infusions, steroids, metoclopramide, and proton-pump inhibitors (Table 4).

Most cases of VAP were caused by Pseudomonas aeruginosa, which accounted for 88.8% of causative organisms (Table 6). Microorganisms isolated in the tracheal aspirates of patients with VAP were P. aeruginosa (n=26, 57.7%), Klebsiella pneumoniae (n=8, 17.7%), Acinetobacter baumanii (n=3, 6.6%), Serratia marcescens (n=3, 6.6%), Staphylococcus aureus MRSA (n=2, 4.4%), and Candida ssp. (n=3, 6.6%). VAP was polymicrobial in 7 patients (15.5%).

Discussions

We conducted a retrospective, observational study to find the incidence, risk factors, and nosocomial germs for ventilator-associated pneumonia (VAP) in mechanically ventilated pediatric patients. Our study population included patients from PICU in an urban pediatric hospital. In the absence of a true gold standard for VAP in children, VAP was defined according to the CPIS, using clinical and biological parameters. CPIS has been used in multiple studies on VAP in adults (9-12), but limited data is available on pediatric patients (13-15). In patients with confirmed VAP, we found a median CPIS score of 8.16, comparable with the values reported in literature (15).

The incidence of VAP among mechanically ventilated children was 43.13%, higher than reported (2,3), but comparable to studies conducted in developing countries (16,17). This can be a reflection of health care of patients.

Like other studies before, our multivariate analysis of risk factors revealed previous use of one ore more antibiotics (p=0.02, respectively p<0.01), antifungal drugs (p=0.05) and reintubation (<0.01) to be positively associated

with the development of VAP (18,19). Aggressive usage of antibiotics and routine periodic change of endotracheal tube should be discouraged.

Several risk factors for the development of VAP identified by other studies such as transfusions, immunoglobulins, narcotics, inotrope infusions, use of gastric stress ulcer prophylaxis were not found to be associated with VAP in our study. This may be due to the fact that we analyzed risk factors temporally related, in the 72-hour period, before a positive endotracheal tube culture and not simply at any time during mechanical ventilation.

Transfusions of different blood products were reported by other studies as risk factors for VAP (20-22). In our PICU, we limit the use of transfusions and immunoglobulins only to patients with sepsis/severe sepsis, and maybe because of the small number of these patients in our study (3 patients non-VAP and 5 patients with VAP), we did not found any association with the occurrence of VAP.

Some studies have identified use of sedation and neuromuscular blockade, to be independently associated with VAP (23,24). The particular association of narcotics with VAP may indicate that gastrointestinal hypomotility secondary to narcotics may be a mechanism for increased risk of VAP via microaspiration of gastric contents. We found no difference in use of sedative agents between patients who developed VAP versus those without VAP, and this is maybe because we used in all patients cuffed endotracheal tubes, witch prevented microaspirations. Similarly, H2 blockers usage was associated with an increased risk as it can alter the gastric pH, thereby facilitating organism multiplication which, when aspirated, can lead to occurrence of VAP. By contrast, probiotics administration reduced the incidence of ICU-acquired pneumonia (25). In our study, we did not found H2 blockers as risk factors for VAP, and the majority of intubated patients received probiotic treatment (data not shown). Data regarding the usage of H2 blockers are controversial. For example, Gautam et al. (26) found in a new research that the absence of tube feeding and the absence of stress ulcer prophylaxis were independent risk factors for VAP.

Other risk factors published before, both in children and adults, but not identified in our study were gender, admission diagnosis, chronic obstructive pulmonary disease, bronchoscopy, tracheostomy, oropharyngeal colonization, prolonged MV, supine body position, tube thoracostomy, enteral feeding, genetic syndrome, and transport out of the PICU (5,14,18,27,28).

The most common bacterial isolates from endotracheal aspirates were Pseudomonas aeruginosa (57.7%), followed by Klebsiella pneumoniae (7.7%). A small number of patients developed VAP with Staphylococcus aureus (4.4%). Pneumonia in pediatric population is often associated with Pseudomonas aeruginosa and Staphylococcus aureus, according to the National Nosocomial Infections Surveillance (NNIS) in the United States (29) and to the European Multicenter Study Group (30).

We found in our study that VAP did not have a serious impact on mortality ($p=0.69$). We also found that patients who developed VAP had longer duration of mechanical ventilation ($p<0.01$) and longer hospital stay ($p<0.01$) than those who did not, which is consistent with other reports (14,16,18,19,26-28).

Conclusions

The incidence of VAP was higher (43%) in our study. Children on previous use of antibiotics or antifungal drugs, or experienced reintubation developed VAP and had a longer period of mechanical ventilation and hospitalization. Pseudomonas aeruginosa was the most common Gram-negative bacteria associated with VAP. Awareness about the various risk factors will aid in reduction of the morbidity associated with VAP. VAP negatively impacts clinical and economic outcomes in critically ill pediatric patients by prolonging the length of mechanical ventilation and hospital stay and may increase total hospital charges.

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References

1. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R, Centers for Disease Control and Prevention, Healthcare Infection Control Practices Advisory Committee. Guidelines for preventing health-care-associated pneumonia, 2003: Recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep. 2004 Mar 26;53(RR-3):1-36.
2. Guidelines for the management of adults with hospital-acquired,ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005,171:388-416.
3. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002;165(7):867-903.
4. Gupta A, Agrawal A, Mehrotra S, Singh A, Malik S, Khanna A. Incidence, risk stratification, antibiogram of pathogens isolated and clinical outcome of ventilator associated pneumonia. Indian J Crit Care Med. 2011 Apr-Jun;15(2):96-101.
5. Xie DS, Xiong W, Lai RP, Liu L, Gan XM, Wang XH, et al. Ventilator-associated pneumonia in intensive care units in Hubei Province, China: a multicentre prospective cohort survey. J Hosp Infect. 2011 Aug;78(4):284-8. Epub 2011 Apr 20.
6. Tejerina E, Frutos-Vivar F, Restrepo MI, Anzueto A, Abroug F, Palizas F, et al. Incidence, risk factors, and

outcome of ventilator-associated pneumonia. J Crit Care 2006,21:56-65.
7. Ak O, Batirel A, Ozer S, Çolakoğlu S. Nosocomial infections and risk factors in the intensive care unit of a teaching and research hospital: a prospective cohort study. Med Sci Monit. 2011 May;17(5):PH29-34.
8. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991;143:1121-9.
9. Su LX, Meng K, Zhang X, Wang HJ, Yan P, Jia YH, et al. Diagnosing ventilator-associated pneumonia in critically ill patients with sepsis. Am J Crit Care. 2012 Nov;21(6):e110-9.
10. Tejerina E, Esteban A, Fernández-Segoviano P, Frutos-Vivar F, Aramburu J, Ballesteros D, et al. Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. J Crit Care. 2010 Mar;25(1):62-8.
11. Pham TN, Neff MJ, Simmons JM, Gibran NS, Heimbach DM, Klein MB. The clinical pulmonary infection score poorly predicts pneumonia in patients with burns. J Burn Care Res. 2007 Jan-Feb;28(1):76-9.
12. Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003 Jul 15;168(2):173-9.
13. Morrow BM, Argent AC. Ventilator-associated pneumonia in a paediatric intensive care unit in a developing country with high HIV prevalence. J Paediatr Child Health. 2009 Mar;45(3):104-11.
14. Srinivasan R, Asselin J, Gildengorin G, Wiener-Kronish J, Flori HR. A prospective study of ventilator-associated pneumonia in children. Pediatrics 2009; 123:1108–1115.
15. Sachdev A, Chugh K, Sethi M, Gupta D, Wattal C, Menon G. Clinical Pulmonary Infection Score to diagnose ventilator-associated pneumonia in children. Indian Pediatr. 2011 Dec;48(12):949-54.
16. Marjanović V, Novak V, Velicković L, Marjanović G. The incidence and risk factors of ventilator-associated pneumonia in patients with severe traumatic brain injury. Med Pregl. 2011 Jul-Aug;64(7-8):403-7.
17. Dey A, Bairy I. Incidence of multidrug resistant organisms causing ventilator associated pneumonia in a tertiary care hospital: 9 months prospective study. Ann Thorac Med. 2007;2:52-7.
18. Bauer TT, Ferrer R, Angrill J, Schultze-Werninghaus G, Torres A. Ventilator-associated pneumonia: incidence, risk factors, and microbiology. Semin Respir Infect. 2000;15:272–279.
19. Awasthi S, Tahazzul M, Ambast A, Govil YC, Jain A. Longer duration of mechanical ventilation was found to be associated with ventilator-associated pneumonia in children aged 1 month to 12 years in India. J Clin Epidemiol. 2013 Jan;66(1):62-6.
20. Roeleveld PP, Guijt D, Kuijper EJ, Hazekamp MG, de Wilde RBP, de Jonge E. Ventilator-associated pneumonia in children after cardiac surgery in The Netherlands. Intensive Care Med. 2011;37:1656-63.
21. Taylor RW, O'Brien J, Trottier SJ, Manganaro L, Cytron M, Lesko MF, et al. Red blood cell transfusions and nosocomial infections in critically ill patients. Crit Care Med. 2006;34(9):2302-08.
22. Shorr AF, Duh MS, Kelly KM, Kollef MH; CRIT Study Group. Red blood cell transfusion and ventilator-associated pneumonia: a potential link? Crit Care Med. 2004;32(3):666-74.
23. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002;165(7):867-903.
24. Fayon MJ, Tucci M, Lacroix J, et al. Nosocomial pneumonia and tracheitis in a pediatric intensive care unit: a prospective study. Am J Respir Crit Care Med. 1997;155(1):162-9.
25. Barraud D, Bollaert PE, Gibot S. Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials. Chest. 2013 Mar;143(3):646-55.)
26. Gautam A, Ganu SS, Tegg OJ, Andresen DN, Wilkins BH, Schell DN. Ventilator-associated pneumonia in a tertiary paediatric intensive care unit: a 1-year prospective observational study. Crit Care Resusc. 2012 Dec;14(4):283-9.
27. Apostolopoulou E, Bakakos P, Katostaras T, Gregorakos L. Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. Respir Care. 2003 Jul;48(7):681-8.
28. Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. Pediatrics. 2002;109(5):758-64.
29. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control.2004;32(8):470-85.
30. Raymond J, Aujard Y; European Study Group. Nosocomial infections in pediatric patients: a European, multicenter prospective study. Infect Control Hosp Epidemiol.2000;21(4):260-3.

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MESENTERIC OXYGEN DESATURATION IN AN NEWBORN WITH INTRAUTERINE GROWTH RESTRICTION AND COMPLEX CONGENITAL HEART DISEASE WHO DEVELOPED NECROTISING ENTEROCOLITIS-CASE PRESENTATION

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Abstract

Congenital heart disease is a major risk factor for the development of necrotising enterocolitis (NEC), although its pathophysiology remains incompletely understood. NEC is a multifactorial disease that occurs in a high risk newborn. NEC incidence is inversely proportional to gestational age, only 10% of term infants develop disease.

We present the case of a term newborn with intrauterine growth restriction and complex congenital heart disease (CHD), who developed in the underlying disease, enterocolitis at 10 days of life. Early diagnosis was established using near-infrared spectroscopy (NIRS) which showed significant mesenteric oxygen desaturation secondary to significant decrease in aortic blood flow.

The standard treatment of NEC with antibiotics, enteral feeding cessation and cardio-circulatory support did not work in this newborn due to decreased mesenteric blood flow and significant ischemia. CHD that caused extremely low blood flow in mesenteric territory and which could not be surgically corrected caused child's death.

NIRS is a noninvasive diagnostic method that monitors highly accurate regional tissue oxygenation and could detect mesenteric ischemia in early stages.

The authors want to emphasize through this rare case of CHD, that any heart disease with decreased aortic flow lead to impaired mesenteric oxygen delivery beeing a risk factor for NEC. Tissue hypoxia secondary to decreases in mesenteric blood flow is the central pathophysiological cause of NEC in this term infant.

We also want to highlight the usefulness of NIRS for noninvasive measurement of tissue perfusion in all high risk neonates.

Keywords: term newborn, intrauterine growth restriction, complex congenital heart disease, necrotising enterocolitis , near-infrared spectroscopy, mesenteric oxygen desaturation.

Introduction

NEC is an inflammatory bowel disease of the newborn, beeing one of the most common gastrointestinal emergency in this age, causing a high mortality rate between 10-30%, surgical cases exceeding 50% (1).

NEC is considered a multifactorial disease that occurs in a high risk newborn. Despite the research conducted for understanding this disease, the pathophysiology of NEC is still incompletely understood. It is believed that involve a complex interaction among several factors: gestational age, infant milk formula, enteral nutrition, functional immaturity of the newborn gut, intestinal hypoxia-ischemia, treatment with antibiotics and the presence of infectious agents or toxins (2). The main pathogenetic link is represented by intestinal ischemia and reperfusion injury with an inadequate inflammatory response (3,4).

NEC incidence is inversely proportional to gestational age, over 90% of affected infants are preterms and only 10% of term infants develop the disease(5.) These term infants often present additional risk factors that may predispose to intestinal ischemia such as CHD, intrauterine growth restriction or asphyxia at birth (6,7,8,9). From CHD, increased risk in developing NEC have the following: obstruction of the aortic arch, hypoplastic left heart syndrome and common arterial trunk (6).

NIRS is a noninvasive, feasible and beneficial technology, that monitors regional tissue oxygenation reflecting the tissues perfuzional status. NIRS has the ability to continuously and simultaneously monitor tissue perfusion in different organs without interrupting pacient's routine care. Studies have demonstrated the efficacy of NIRS to monitor cerebral, intestinal and renal perfusion, to detect potential ischemic episodes. NIRS can help other monitoring methods currently used, to increase the degree of suspicion of abnormal perfuzional status in infants and thus reduce the risk of developing ischemic lesions (10,11,12,13).

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It utilizes light wavelengths (700-1000nm). The technique consists in placing probes on different areas of the body such as the forehead (cerebral), abdomen (mesentery) and lower back (renal). Each probe consists of a light source and 2 photodetectors to measure tissue oxygen levels at different tissue depths. One path length measures surface level tissue oxygenation and the other path length measures deep tissue oxygenation. The photons emitted from the light source scatter in the tissue bed and those that are not absorbed are returned to the skin photodetector. By measuring the amount of light (deep path minus surface path) returned to the skin, NIRS values represent the amount of spectral absorbtion that is occuring in the tissue bed. This measurement represents the weighted average of arterial, venous and capillary oxygenation at the tissue level and is reported as regional oxygen saturation (rSo2). In this way, the clinician can monitor directly, in real time, fluctuations in tissue oxygenation (14).

Case presentation

We present the case of a female newborn, the second child of young, healthy parents, undispensarized pregnancy , born at home, assisted by midwife, with gestational age of 39 weeks and birth weight 2300 grams. No significant family history. The child is brought in Neonatology Department of Emergency Municipal Hospital Timisoara 1 hour after birth. He presented good general status at birth, with good neonatal adaptation.

On the 6th day of life begins to present impaired general condition, hypotonic, pale, mottled skin, abdominal distension, hypothermia, cold extremities, prolonged capillary refill time, barely perceptible pulse, systolic murmur grade 1, cyanosis. The child develops respiratory distress syndrome with high oxygen necessary that worsen quickly, SaO2 reached 45% with FiO2> 50%.

It was initially diagnosed as a possible septic shock by infection with unknown germs. Has been decided intubation and mechanical ventilation, with improvement in oxygen saturation, then no episodes of desaturation. After 24 hours the clinical status of the baby has improved consistently, so we decided to detubate him. We administerd him oxygen under chefalic cort with a minimal FiO2 of 30% throughout the monitoring period. Since we have excluded the septic component of the neonatal shock, we performed an echocardiography.

Echocardiography showed interrupted aortic arch with ensuring blood flow in the descending aorta through the ductus arteriosus, wide ventricular septal defect, patent foramen ovale, severe pulmonary hypertension, suprahepatic veins and inferior vena cava dilatation (Figure 1).

Considering CHD presenting decreased aortic flow and therefore decreased mesenteric flow, we decided to initiate monitoring of regional cerebral and mesenteric oxygenation through near-infrared spectroscopy. One probe was placed on the abdomen child on the midline, below the umbilicus and above the pubic symphysis to measure regional mesenteric oxygenation and second probe was placed on the right side of the forehead to measure cerebral oxygen saturation. (Figure 2).

On the 9th day of life the baby begins to present digestive symptoms with gastric residue containing milk then bilious content, increased abdominal diameter, hepatosplenomegaly, without bowel movements, no femoral artery pulse. All this clinical symptoms raises the suspicion of NEC onset. Abdominal X-ray reveals intestinal air- fluid levels with intestinal pneumatosis without pneumoperitoneum (Figure 3). We established the diagnosis of NEC.

We stoped enteral nutrition and we instituted antibiotic therapy. Biological samples did not reveal thrombocytopenia, significant acidosis or bacterial infection. Continuous monitoring of mesenteric oxygenation highlights significant decrease in oxygen saturation (rSO2 = 25.2% ± 8.9%) compared with cerebral oxygenation (rSO2 = 72% ± 5%) during the monitoring period ($p < 0.0001$) (Figure 4).

As specific therapy it is tried by medication to keep open the ductus arteriosus, and decreasing pulmonary hipertension by selective pulmonary vasodilatory therapy (to decrease blood flow in the pulmonary circulation and increased mesenteric blood flow).

Despite the instituted therapy, after a short period of improvement of clinical symptoms and biological parameters, clinical status of the child deteriorates progressively with cardiorespiratory decompensation and worsening digestive symptoms, he died at 17 days of life (Table 1).

Discussion

NIRS has been used extensively to monitor cerebral perfusion in neonates, especially during cardiac surgery and cardiopulmonary bypass. More recently, it has been reported using of NIRS to measure perfusion in other tissues, such as those of the liver, the kidneys, and the lower abdomen (15,16,17).

In a study conducted by Fortune and his collaborators it was revealed the association between NEC and mesenteric oxygen desaturation. They monitored 40 neonates, 10 who had acute surgical abdomen (including 5 with NEC) and 30 neonates without abdominal pathology and they watched the changing of mesenteric-to-cerebral oxygenation ratios. The results showed that the control group had an median ratio of 0.96 while the study group had a much lower ratio of 0.66 ($P < 0.001$).The authors also reported that a ratio of less than 0.75 was predictive for intestinal ischemia (positive predictive value) and that a ratio of 0.96 or more excluded the diagnosis (17).

Stapleton and colleagues presented a case like ours, highlighting the significantly mesenteric oxygen desaturation measured by NIRS, in a newborn with CHD, that developed NEC (18).

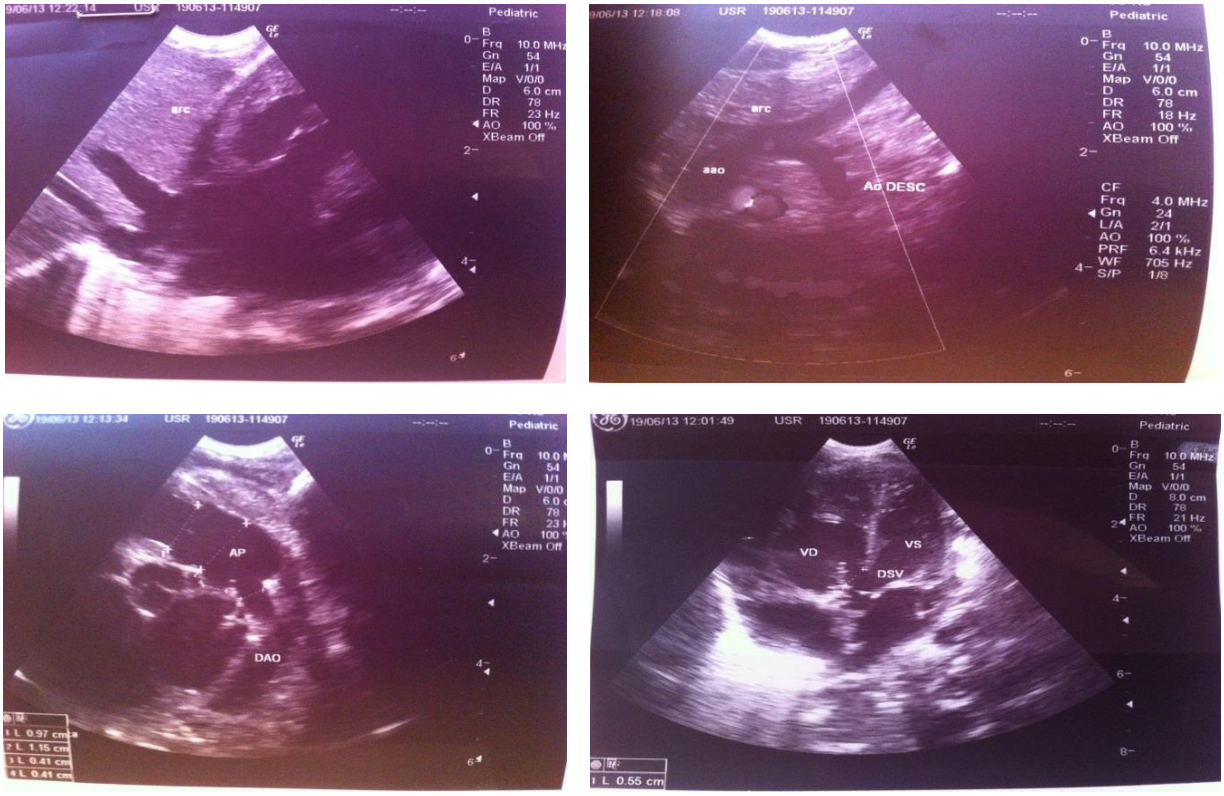

Figure 1. Echocardiography shows interrupted aortic arch, dilated pulmonary artery, wide ventricular septal defect.

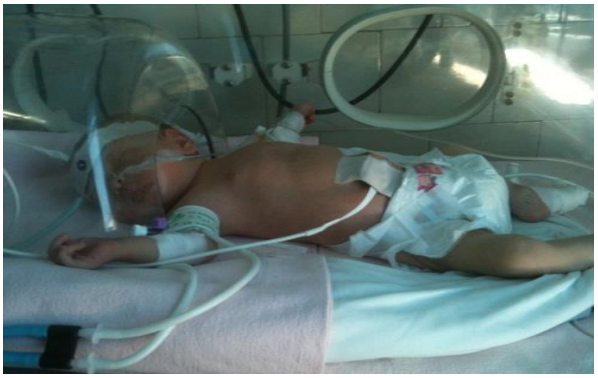

Figure 2. The two positions of spectroscopy probes: cerebral and abdominal.

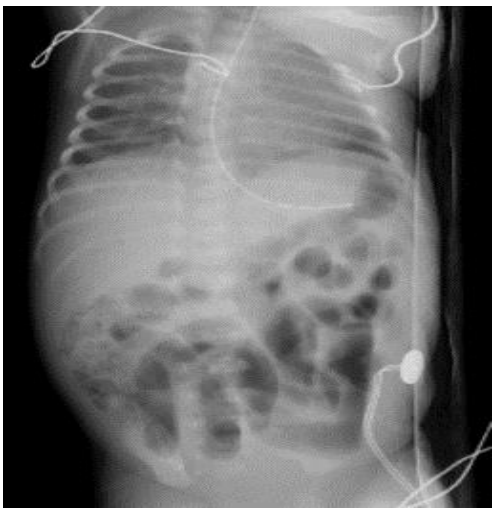

Figure 3. The X-ray reveals the appearance of NEC.

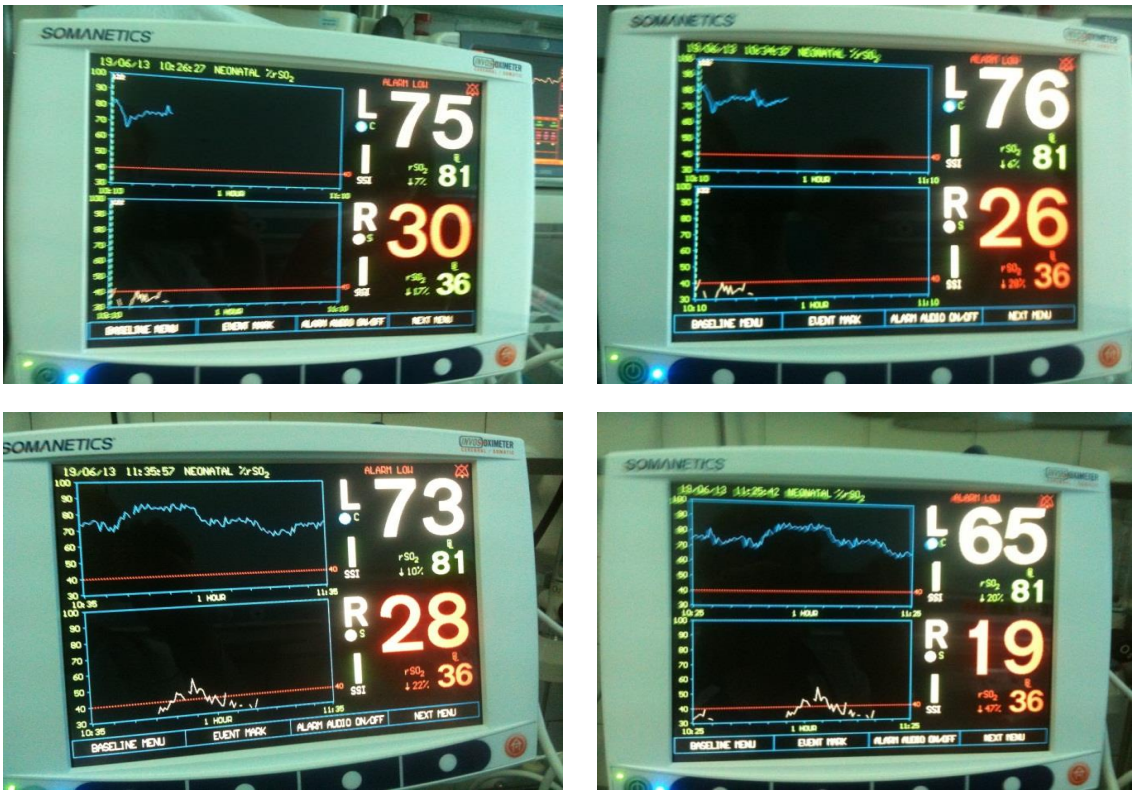

Figure 4. Regional cerebral and mesenteric oxygen saturation, measured by near-infrared spectroscopy after diagnosis of NEC.

Parameters	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 16	D 17
SaO2 %	96	95	97	95-97	89-95	85-92	83-92	<85	70-40
BP mmHg	83/60	80/60	115/75	100/70	62/41	130/73	80/60	82/55	70/50
HR b/min	141	125	150	160	150	165	172	175	180-60
D ml /24h	42	50	100	80	115	56	30	24	6
rSO2c	75	75	76	73	67	68	65	67	65
rSO2s	35	30	26	28	23	23	19	0	0

Table 1. The patient's vital parameters monitored from the time of NEC diagnosis until death.SaO2 = arterial oxygen saturation, BP = blood pressure, HR=heart rate , D = diuresis, rSO2c = regional cerebral oxygen saturation, rSO2s = somatic regional oxygen saturation, D = day

It is unknown whether gut ischemia is a primary or secondary factor in the development of NEC, but the finding that our patient experienced significant mesenteric desaturation during the early stages of NEC supports the hypothesis that tissue hypoxia is central to the pathophysiology of NEC, especially in term neonates with CHD.

The development of mesenteric desaturation may be due to decreased regional oxygen delivery that is secondary to decreased cardiac output and/or increased flow to the pulmonary vascular bed.

Conclusions

NIRS is a noninvasive, highly accurate, diagnostic method, that detects mesenteric ischemia in early stages. A specific target therapy for NEC in this phase may be saving.

The authors want to emphasize through this rare case of CHD, that any heart disease with decreased aortic flow lead to impaired mesenteric oxygen delivery beeing a risk factor for NEC. Tissue hypoxia secondary to decreases in mesenteric blood flow is the central pathophysiological cause for NEC in this term newborn.

Using this technology, of the near-infrared spectroscopy , for non-invasive measurement of tissue

oxygenation in high risk neonates, it is likely that understanding and therapy management of these patients to improve.

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References

1. Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet. 2006;368:1271–1283.
2. Sheila M. Gephart, Jacqueline M. McGrath, Judith A. Effken, Melissa D. Halpern. Necrotizing Enterocolitis Risk: State of the Science. Advances in Neonatal Care.April 2012; 12(2): 77 – 87.
3. Claud EC, Walker WA. Hypothesis: inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis. FASEB J.2001;15 (8):1398-1403.
4. Markel TA, Cristostomo PR, Wairiuko GM, et al. Cytokines in necrotizing enterocolitis. Shock.2006;25(4):329-337.
5. Schnabl KL, Van Aerde JE, Thomson ABR, Clandinin MT. Necrotizing enterocolitis: A multifactorial disease with no cu cure. World J Gastroenterol 2008; 14(14): 2142-2161.
6. McElhinney DB, Hedrick HL, Bush DM, Pereira GR, Stafford PW, Gaynor JW, et al. Necrotizing enterocolitis in neonates with congenital heart disease: risk factors and outcomes. Pediatrics 2000;106:1080–7.
7. Maayan-Metzger A, Itzchak A, Mazkereth R, Kuint J. Necrotizing enterocolitis in full-term infants: case-control study and review of the literature. J Perinatol 2004;24:494–9.
8. Ostlie DJ, Spilde TL, St Peter SD, Sexton N, Miller KA, Sharp RJ, et al. Necrotizing enterocolitis in full-term infants. J Pediatr Surg 2003;38:1039–42.
9. Bolisetty S, Lui K, Oei J, Wojtulewicz J. A regional study of underlying congenital diseases in term neonates with necrotizing enterocolitis. Acta Paediatr 2000;89:1226–30.
10. Terri Marin, James Moore. Understanding near-infrared spectroscopy. Advances in Neonatal Care 11(6):382 (2011).
11. Petrova A, Mchta R. Near-infrared spectroscopy in the detection of regional tissue oxygenation during hypoxic events in preterm infants undergoing critical care. Pediatr. Crit. Care Med. 2006;7(5):449-454.
12. McNeill S, Gatenby JC, McElroy S, Engelhardt B. Normal cerebral, renal and abdominal regional oxygen saturation using near-infrared spectroscopy in preterm infants. J Perinatol. 2011; 32(1):51-57.
13. Tortoriello TA, Stayer SA, Mott AR, McKenzie ED, Fraser CD, Andropoulos DB, Chang AC. A noninvasive estimation of mixed venous oxygen saturation using near-infrared spectroscopy by cerebral oximetry in pediatric cardiac surgery patients. Paediatr Anaesth 2005;15:495–503.
14. Dullenkopf A, Frey B, Baenziger O, Gerber A, Weiss M. Measurement of cerebral oxygenation state in anaesthetized children using the INVOS 5100 cerebral oximeter. Paediatr. Anaesth. 2003; 13(5):384-391.
15. Weiss M, Schulz G, Teller I, Dullenkopf A, Kolarova A, Sailer H, et al. Tissue oxygenation monitoring during major pediatric surgery using transcutaneous liver near infrared spectroscopy. Paediatr Anaesth 2004;14:989–95.
16. Hoffman GM, Stuth EA, Jaquiss RD, Vanderwal PL, Staudt SR, Troshynski TJ, et al. Changes in cerebral and somatic oxygenation during stage 1 palliation of hypoplastic left heart syndrome using continuous regional cerebral perfusion. J Thorac Cardiovasc Surg 2004;127:223–33.
17. 17. Fortune PM, Wagstaff M, Petros AJ. Cerebro-splanchnic oxygenation ratio (CSOR) using near infrared spectroscopy may be able to predict splanchnic ischaemia in neonates. Intensive Care Med 2001;27:1401–7.
18. Gary E. Stapleton, Brian K. Eble, Heather A. Dickerson, Dean B. Andropoulos, Anthony C. Chang. Mesenteric Oxygen Desaturation in an Infant with Congenital Heart Disease and Necrotizing Enterocolitis. Tex Heart Inst J. 2007; 34(4): 442–444 .

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PHARMACOGENETIC ASPECTS WHICH INFLUENCE THE PHARMACOKINETIC PROPERTIES OF ATYPICAL ANTIPSYCHOTICS – PRELIMINARY STUDY

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Abstract

Patients under medical treatment show significant differences in treatment response. Among the reasons of this variability, the genetic factors play an important role. Pharmacogenetics is a new science, at the crossroads between pharmacology and genetics, which studies how genes polymorphism influences inter-patient variability in drug response, in terms of efficacy and side effects profile. The existence of a large number of schizophrenic patients showing resistance to antipsychotic treatment requires the development of such methods that could be able to predict the individual responsiveness to antipsychotics treatment. The ability to predict treatment response based on gene variation aims to optimize drug therapy by prescribing the most effective drug in the right dose and with the lowest risk of side effects. This paper highlights the current knowledge about the clinical utility of determining the genetic factors that may affect the metabolism of atypical antipsychotics. The paper does not want to present an exhaustive list of all pharmacogenetic studies in the field, but is focused on the most studied examples of DNA sequence variations in genes that encode cytochrome P450 enzymes, in relation to treatment response. Pharmacokinetic studies were identified by means of combinations of the keywords in the Pub Med database.

Keywords: antipsychotics, pharmacogenetics, polymorphisms, cytochrome P450.

Introduction

Atypical antipsychotics are a class of drugs that have as main indications schizophrenia and bipolar disorder. Since clozapine, the prototype of this class, which was introduced in medical practice in 1989, various novel compounds have entered the market: risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone. Compared to classical antipsychotics, they have a number of benefits: reduced risk of extrapyramidal syndrome, superior efficacy for improving negative symptoms, treatment of refractory cases and little effect on prolactin secretion. These advantages are considered to be due to the dual antagonism of the dopaminergic and serotoninergic system. The atypical antipsychotics have of course their own side effects: weight gain, predominantly for clozapine and olanzapine, hyperlipidemia and hyperglycemia. Over time it was observed that for the same antipsychotic given in the same dosage there is a wide variation from patient to patient regarding length of the onset of action, intensity of pharmacological action and severity of side effects. Thus, the current research directions are oriented towards understanding the interindividual variability of treatment response in order to customize and optimize drug choice.

With the completion of the Human Genome Project, researchers became interested in the genetic differences between humans and identification of those genes that have an impact on health status.

The fact that patients respond differently to antipsychotic treatment is largely due to the different genetic imprinting existing between one another. Psychiatric pharmacogenetics aims to identify the genetic inheritance of a patient and how this influences drug treatment outcomes.

Most pharmacogenetic research conducted in the field, uses as strategy the candidate gene approach, that explores the association between an allelic variation of candidate gene and the characteristic of interest (such as treatment response). This requires knowledge of the pharmacology of antipsychotics in order to select those genes that encode proteins that the drug interacts with in the course of the pharmacokinetic process (cytochrome-P450 enzymes, plasma binding protein, transport protein, etc.) or of the pharmacodynamic process (receptors, enzymes, etc.). Subsequently, the molecular genetic techniques can establish the existence of genetic polymorphisms (variations) in these genes of interest which might be responsible for phenotypic differences. This means that a certain gene in the form of an allele determines a certain type of treatment response, while another allele of the same gene, may generate an altered response.

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The discovery of pharmacogenetic markers that influence antipsychotic pharmacodynamics, with strong predictive value for clinicians, is difficult because the mechanism of drugs action involves multiple proteins and second messengers, and each of them can be subject to genetic variability.

By now, the greatest progress made in antipsychotic therapy individualization based on molecular diagnosis, is represented by cytochrome P450 genotyping. Since most antipsychotics are metabolized by cytochrome P450 enzymes, the existence of genetic variation affecting the enzymatic activity will influence the plasma concentration of antipsychotics, and therefore the efficacy and tolerability of medication.

Material and method

Prior to inclusion in this study, informed consent was obtained from each subject. A special attention was given to protect the privacy of the subjects. This study respected the guidelines which regalements the utilization of patients data and the use of patients DNA samples in research use.

A lot of 50 patients were selected for molecular genetic investigations. Inclusion on the study lot was made based on several criteria. Were selected patients who undergo treatment with aripiprazol and risperidone.

An evaluation form was established and applied for all the patients who undergo treatment with the above mentioned drugs. It were collected dates about the age at which the individual first experienced a diagnosis or symptoms of schizophrenia. The severity of manifestations was established based on the PANSS score. Different grades were used in order to correlate the severity of each symptom (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 =severe, 7 = extreme). For each patient from the study lot, PANSS score before initiation of the treatment was available. In order to evaluate the therapeutic effect, PANSS assessments at 1, 3 and 6 month after initiation of anti-psychotic treatment was done.

The patients selected for study were divided in 2 sub-lots based on the PANSS score evolution. Those who presented clinical improvement of the manifestation, based on the PANSS score were included in sub-lot 1 which served as a reference lot. The second lot included patients that did not exhibit the expected evolution in clinical manifestations.

For each patient 2 mL of venous blood was collected using a heparinized blood collection tube. The DNA extraction was done by using the commercial DNA extraction kit (Qiagen Mini DNA Extraction kit). In this study, the CYP2D6 alleles, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6 were selected for detection based on the frequencies of those polymorphism in Caucasian population.

For the CYP2D6 SNPs genotyping, we choose the TaqMan® Pre-Developed Assay for Allelic Discrimination Kit (Applied Biosystems). Amplification and analysis of patients' samples are run on a 7500 Real-time PCR sistem (Applied Biosystems).

The first stage of the study had the purpose of selecting the cohort of patients under treatment with risperidone and aripiprazole, followed by identification of sublots based on the clinical evolution after the therapy, selection of the polymorphisms that will be evaluated, DNA samples preparation as well as the optimization of the protocol for SNPs identification. The second part of the study includes SNPs evaluation and statistical analysis of the results. Statistical analysis has the purpose of evaluating the existence of a positive or negative correlation between the presence of a specific genotype and the PANSS score evolution after treatment institution.

Discutions

Cytochrome P450 iso-enzymes are found primarily in the endoplasmic reticulum of hepatocytes, but are also present in the gut and brain. They are involved in phase I reactions of the hepatic biotransformation of antipsychotics, and are responsible for the modification of functional groups by oxidation reactions that increase hydrophilicity of molecules, in order to eliminate them from the body. Each CYP enzyme is the product of a particular gene. The occurrence of genetic mutations in the gene, will produce different allelic variants of that gene. Allelic variants will encode CYP enzyme variants with different degrees of activity. When genetic mutation occurs with a frequency greater than 1% in the population is called a genetic polymorphism. The most polymorphic izoforms are CYP2D6, CYP3A4, CYP2C19 (1). Following the characterization of patients' genetic profile in relation to polymorphic forms of these enzymes, genotype-phenotype correlations can be established. For example, based on allelic variants of P450 CYP2D6 gene, four phenotypes have been identified:

• "ultrarapid metabolisers" are patients with allelic variants encoding highly functional enzymes

• "intermediate metabolizers" and "poor metabolisers" are patients with allelic variants coding for enzymes with deficient or dysfunctional activity

• "extensive metabolizers", are patients with wild-type allelic variants, with the highest frequency in the population, which have normal enzymatic activity.

Atypical antipsychotics have primary and secondary pathways of biotransformation. These should be well known in order to properly assess the clinical relevance of polymorphisms (Table 2) (3). For a poor metaboliser CYP2D6, prescribing an antipsychotic such as aripiprazole, iloperidone, paliperidone or risperidone, which are extensively metabolized by this particular isoenzyme, should be avoided. If there is no therapeutic alternative available, it is recommended to reduce their doses.

Until recently, the way in which the optimal dose of antipsychotic could be determined, with clinical efficacy and minimal risk of adverse effects, was by regular determination of drugs plasma levels, but this required repeated blood sampling. Conducting a therapy using pharmacogenetic testing has the advantage of anticipation of plasma levels, before antipsychotic administration, so that the initiation of therapy should be judiciously done. For

example, Hendset et al. recommends for CYP2D6 poor metabolisers patients, a 30-40% reduction of the maximum aripiprazole daily dose, so that they reach the same steady state concentration of aripiprazole and dehidroaripirazole (the active metabolite) as extensive metabolisers (4).

Genotype	Phenotype	Consequences at usual recommended dosage of active drugs	Frequency in the Caucasian population (%) (2).
Gene duplication in absence of inactive or low activity allele	ultrarapid metabolisers	- subtherapeutic plasma levels - therapeutic ineffectiveness	2
Two alleles (wild-type) with normal activity	extensive metabolizers	- therapeutic plasma levels - clinical efficacy	80
Two low-activity allele *or* carriers of one active allele and one inactive *or* one low-activity allele and one inactive	intermediate metabolizers	- increased plasma concentrations - adverse effects, toxicity - biotransformation in another unfavorable pathway - reduced prodrug activation	10
Two inactive alleles	poor metabolisers	- increased plasma concentrations - adverse effects, toxicity - biotransformation by another unfavorable pathway - lack of prodrug activation	8

Active alleles * 1, * 2, * 33, * 35

Low activity alleles * 9, * 10, * 17, * 29, * 36, * 41

Inactive alleles * 3 - * 8 * 11 - * 16, * 19 - * 21, * 38, * 40, * 42

Table 1. CYP2D6 genotype-phenotype relationship

Not always pharmacogenetic studies have led to recommendations for clinical practice, because many of them have failed to achieve significant results.

In 1995, Arraz et al. undertook one of first studies on correlation between the CYP2D6 genotype and response to antipsychotic treatment. The study included 130 Caucasian patients that had been undergoing treatment with clozapine. They observed that poor metabolisers and ultrarapid ones were equally distributed in the 2 groups of patients - responsive and non responsive to treatment -, failing to establish a correlation between CYP2D6 genotype and drug response (5). This may however be due to the fact that CYP2D6 is a minor metabolic pathway for clozapine, the maijor being CY1A2. It goes without saying that the poor metaboliser phenotype in a minor metabolic pathway will have a lower impact on treatment response as compared with the poor metaboliser phenotype in a major metabolic pathway. Also, one pharmacogenetic study of Melkerson et al. failed to establish an association between the poor and intermediate CYP2D6 metaboliser phenotype and plasma levels of clozapine and its metabolite N-desmetilclozapina. Instead, CYP1A2 poor metabolisers (major route of metabolism of clozapine) have higher plasma concentrations and a higher risk of hyperlipidemia and increased insulin resistance (6).

Atypical antipsychotic	CYP2D6	CYP3A4	CYP1A2
Aripiprazole	+++	+	
Clozapine	+	+	+++
Iloperidone	+++	+	
Olanzapine	+		+++
Paliperidona	+++	+	
Quetiapine		+++	
Risperidone	+++	+	
Ziprasidone		+	

Table 2. CYP450 enzymes responsible for metabolism of atypical antipsychotics.

Once genotyping of cytochrome P450 became possible, Dutch Pharmacogenetics Working Group of Royal Dutch Pharmacist Association, based on current research evidence, recommends testing of P450 genotype in order to individualize therapeutic doses of:

• aripiprazole: reduction of the maximum dose to 10 mg / day (67% maximum recommended daily dose) for CYP2D6 poor metabolisers;

• risperidone: in poor, intermediate or ultrarapid CYP2D6 metabolisers, administration of an alternative drug is recommended (eg, quetiapine, olanzapine, clozapine) or careful monitoring of side effects and adjustment of dose based on clinical response. Information from pharmacogenetic studies is insufficient to determine the exact optimal dose (7).

In the list of drugs that have included pharmacogenetic information in their lables, Food and Drug Administration (FDA) included aripiprazole, clozapine, iloperidone, risperidone. The biomarker that is referred to is CYP2D6. In CYP2D6 poor metabolizer patients, for aripiprazole and iloperidone, a 50% reduction of the initial dose is recommended, with subsequent dosage adjustment based on the clinical response. Also, reducing the dose of clozapine is recommended, without specifying the exact percentage (8).

Another advantage of pharmacogenetic testing, prior to administration of an antipsychotic, is the possibility to protect the patient from drug-drug interactions that can have serious consequences. The cytochrome P450 enzyme system can be disrupted by factors such as cigarette smoke, alcohol but also drugs. There are drugs (e.g. antiepileptics, antiretrovirals etc.) with enzyme induction effect, which increase the enzymatic activity and accelerate the hepatic biotransformation of the co-administered drug (this case, an atypical antipsychotic), reducing its plasma concentration. This induction leads to diminishing or annulment of the therapeutic effect of the atypical antipsychotic drug. Other drugs that have enzyme inhibition effect (e.g. macrolides), leads to a decrease in rate of hepatic biotransformation of the atypical antipsychotic, causing increased plasma half-life, with the risk of accumulation and occurrence of toxic effects from overdose. (9) This types of drug interaction can turn an extensive metabolizer into a rapid one (by enzymatic induction) or into an intermediate/poor one (by enzymatic inhibition).

In 1999, Markowity et al. noted that the association of ciprofloxacin with olanzapine causes the doubling of plasma concentrations of olanzapine, effect due to CYP1A2 enzyme inhibitory activity of ciprofloxacin (10). In 2006, the case of a 70 years old patient was presented, that underwent chronic treatment with azathioprine, vasartan and olanzapine, to whose therapeutic regimen ciprofloxacin (800 mg / day) and furosemide were introduced. After 3 days, the patient experienced a prolongation of 610 ms of the QT interval, which gradually returned to normal after replacing ciprofloxacin with a cephalosporin. This iatrogenic prolongation of the QT interval may be caused by ciprofloxacin administration itself or may be due to the cumulative effect of ciprofloxacin and olanzapine. Ciprofloxacin has a CYP1A2 enzyme inhibition effect on olanzapine, which causes accumulation of unmetabolised olanzapine, with the risk of adverse effects, including prolongation of QT interval (11). There is no information about the CYP1A2 phenotype of the patient. As a rule, the effects of enzymatic inhibition interaction are more severe if the patient is a poor metabolizer.

Aripiprazole is metabolized via CYP2D6 and CYP3A4. Thus, if initial aripiprazole doses in patients how are CYP2D6 poor metabolizers have to be decreased by 50%, they will be reduced to 25% if the patient is concomitantly under treatment with a potent CYP3A4 enzyme inhibitor (e.g. ketoconazole) (12).

Most studies on pharmacokinetic aspects of pharmacogenetics of atypical antipsychotics have focused on the influence of cytochrome P450 genotype on plasma concentrations of drug and its active metabolite, which were correlated with treatment response.

Studies attempting direct correlation between cit. P450 polymorphisms and clinical efficacy of the treatment are fewer and most of them have negative results. After failure of Arranz et al. to establish such a correlation, Riedel and his collaborators assessed the influence of CYP2D6 genotype on the plasma concentrations of risperidone and 9-HO-risperidone (active metabolite) and the relationship with clinical efficacy. Efficacy was defined as 30% reduction of the PANSS score (positive and negative syndrome scale) after 6 weeks of treatment. Although CYP2D6 *4 allele carriers, (associated with reduction of enzyme activity) showed an increase in plasma levels of risperidone and its active metabolite, the polymorphism could not be correlated with efficacy of treatment defined by the PANSS score (13). In 2008, Thomas P. published a study which also fails to associate the efficacy of olanzapine treatment with CYP2D6*4, CYP1A2*1C, CYP1A2*1F polymorphisms (14). Although cit. P450 phenotype influences plasma drug concentration, more studies are needed to assess consequences from the clinical point of view.

Promising progress is made in CYP genotyping to assess propensity to obesity induced by atypical antipsychotics. Ellingrot et al. have established a relationship between CYP2D6 polymorphisms and weight gain for 11 patients that were under olanzapine treatment. Patients with genotypes *1/*3 and *4, associated with the status of poor metabolizers, had a higher increase of body mass index as compared to carriers of the wild type allelic variant (*1/*1) (15). These results are supported by the study of Lane et al., conducted over 123 ethnic Chinese schizophrenic patients. The presence of CYP2D6 188-C/T polymorphism (CYP3D6 *10 - reduced enzyme activity) was associated with a greater increase in weight after 6 weeks of monotherapy with risperidone, as compared to the homozygotes wild-type (16).

Recently AmpliChip CYP450 (Hoffmann-LaRoche, 2003), the first pharmacogenetic test was approved by the U.S.A. and the European Union allowing identification of CYP2D6 and CYP2C19 gene polymorphisms in order to assess the patients' metabolizer status. Although molecular diagnosis technology has advanced, genotyping for P450 cytochrome is not usually integrated into clinical practice. The physicians often resort to pharmacogenetic testing only when pharmacokinetic parameters are so much modified that there are problems in clinical practice.

Conclusions

We have done a literature overview regarding the role of CYP450 polymorphisms in anti-psychotic treatment response and we believe that our study is justified by the lack of information about the frequency of specific genotypes in the Romanian population and their impact in establishing the best treatment and the correct dose of anti-psychotics.

In any case, even if phenotyping of enzymatic status is useful for predicting plasma concentration of antipsychotics and of active metabolites and to make recommendations on therapy starting and dosage, further future studies are needed so that pharmacokinetic aspects of pharmacogenetics of antipsychotics should find applicability in the exact anticipation of treatment response from a clinical point of view. What is certain is that the future holds an important place to psychofarmacogenetics in therapeutic management and personalized therapy.

References

1. By Julio Licinio (Editor), Ma-Li Wong (Editor) Pharmacogenomics: The Search for Individualized Therapies Publisher: Wiley-VCH | ISBN: 3527303804 | edition 2002 ISBN: 3527303804 Edition: 1 Pub. Date: May 2002 Publisher: Wiley, John & Sons; 390
2. Nadine Cohen (Editor), Pharmacogenomics and Personalized Medicine (Methods in Pharmacology and Toxicology) (Hardcover),2008; 83
3. Ravyn D, Ravyn V, Lowney R, Nasrallah HA. CYP450 Pharmacogenetic treatment strategies for antipsychotics: A review of the evidence. Schizophr Res. 2013 Sep;149(1-3):1-14.
4. Hendset M, Hermann M, Lunde H, Refsum H, Molden E.Impact of the CYP2D6 genotype on steadystate serum concentrations of aripiprazole and dehydroaripiprazole. Eur J Clin Pharmacol 2007;63:1147-51
5. Arranz MJ, Dawson E, Shaikh S, Sham P, Sharma T, Aitchison K, et al.Cytochrome P4502D6 genotype does not determine response to clozapine. Br J Clin Pharmacol 1995;39:417-20
6. Melkersson KI, Scordo MG, Gunes A, Dahl ML Impact of CYP1A2 and CYP2D6 polymorphisms on drug metabolism and on insulin and lipid elevations and insulin resistance in clozapine-treated patients. J Clin Psychiatry. 2007 May;68(5):697-704.
7. http://www.pharmgkb.org/page/dpwg
8. US Food and Drug Administration 2013, Table of Pharmacogenomic Biomarkers in Drug Labels, http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm, accesed August 10, 2013)
9. Cristescu C., Pharmacy clinique, ed. Eurobit, Timişoara, 2013; 63-69
10. Markowitz JS, DeVane CL. Suspected ciprofloxacin inhibition of olanzapine resulting in increased plasma concentration. J Clin Psychopharmacol1999;19:289-91.
11. Konstantinos P. Letsas, Antonios Sideris, Stavros P. Kounas, Michalis Efremidis, Panagiotis Korantzopoulos, Fotios Kardaras Drug-induced QT interval prolongation after ciprofloxacin administration in a patient receiving olanzapine International Journal of Cardiology, Volume 109, Issue 2, 10 May 2006, Pages 273-274
12. US Food and Drug Administartion, Prospect aprobat Aripiprazole la 30.07.2013, (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/

021436s037,021713s029,021729s021,021866s022lbl.pdf , accesed August 11, 2013)
13. Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Müller-Arends A, Weber K, Zach J, Müller N, Möller HJ. Risperidone plasma levels, clinical response and side-effects. Eur Arch Psychiatry Clin Neurosci. 2005 Aug;255(4):261-8
14. Pramod Thomas, Vibhuti Srivastava, Anuradha Singh, Priya Mathur, Vishwajit L. Nimgaonkar, Bernard Lerer, B.K. Thelma Correlates of response to Olanzapine in a North Indian Schizophrenia sample, Psychiatry Research, Volume 161, Issue 3, 15 December 2008, Pages 275-28
15. Ellingrod VL, Miller D, Schultz SK, et al. CYP2D6 polymorphisms and atypical antipsychotic weight gain. Psychiatr Genet. 2002;12:55–58.
16. Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Lu CT, Chang WH. Risperidone related weight gain: genetic and non genetic predictors, J Clin Psychopharmacol. 2006 Apr;26(2):128-34

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RETINOPATHY OF PREMATURITY - RISK FACTORS FOR EVOLUTION

Ramona Albulescu[1], Florina Stoica[1], Nicoleta Andreescu[1], Maria Puiu[1]

Abstract

Retinopathy of prematurity (ROP) is a disorder characterised by abnormal retinal vascular development, and several risk factors are involved. The condition may be in mild form or it may result in retinal detachment which may eventually cause blindness. The management of the risk factors involved in the disease etiopathogenesis and the treatment by laser photocoagulation performed in early stages of the disease are important factors that contribute to less premature infants with retinopathy of prematurity.

Key words: retinopathy of prematurity, risk factors, retinal detachment

Introduction

Retinopathy of prematurity (ROP) is a disorder characterised by abnormal retinal vascular development due to the disorganized growth of retinal blood vessels and several risk factors are involved. ROP affects prematurely-born babies with low birth weight. The incidence of the retinopathy of prematurity is inversely related to the gestational age and the weight at birth. The condition may be in mild form or it may result in retinal detachment, which may eventually cause blindness. (1)

Retinopathy of prematurity may be described according to location, stage and extent (1,2).

For the purpose of defining the location, three concentric zones were defined, centred on the optic disc:

- zone I: a circle, the radius of which extends from the centre of the optic disc to twice the distance from the centre of the optic disc to the centre of the macula,

- zone II: retinal zone which extends centrifugally from the edge of zone I to the nasal ora serrata (at 3 o'clock in the right eye and 9 o'clock in the left eye), the circle reaching the area of the anatomical equator on the temporal side.

- zone III: the residual crescent-moon retina, anterior to the edge of zone II.(1,2)

According to extent, retinopathy of prematurity is quantified as number of clock-hours of involvement, as if the top of the eye were 12 on the face of a clock. Therefore, pathology at the 3 o'clock position corresponds to the right and nasal side of the right eye and the temporal side of the left eye, while the 9 o'clock position corresponds to the left and temporal side of the right eye and the nasal side of the left eye, as the examiner looks at the patient's eyes (1,2).

There are several stages of retinopathy of prematurity:

- stage 0: the retinal vascularisation is incomplete or "immature";

- stage 1: a thin, but well-defined white division line, at the junction between the posterior vascularised and anterior avascular retina. There may also be noticed an abnormal vascular tortuosity, stopping at the division line;

- stage 2: an elevated ridge, specific to the stage 2, replacing the line. It is characterised by volume in height and width, extending out of the plane of the retina. The ridge may change colour from white to pink, and the vessels may proliferate outside the plane of the retina, beyond the ridge and into the vitreous. It should be noted that the presence of these retinal vessels, elevated outside the plane of the retina and into the ridge, do not represent a posterior retina detachment.

Sometimes, small isolated tufts of neovascular tissue lying on the surface of the retina, commonly called "popcorn" may be seen posterior to this ridge structure. These do not constitute the degree of fibrovascular growth that is a necessary condition for stage 3;

- stage 3: extraretinal fibrovascular proliferation or neovascularization, specific to stage 3, is mainly localised as follows: a) continuous with the posterior edge of the ridge, causing a ragged appearance of the ridge; b) into the vitreous, perpendicular to the plane of the retina; c) immediately after the posterior edge of the ridge, however not always connected to it;

- stage 4: partial retinal detachment, which can be further divided into: stage 4A, which includes extra-foveal retinal detachment, and stage 4B, where the partial retinal detachment includes the fovea. Stage 4 retinal detachments are generally concave and most are circumferentially oriented. Its localization and extent need further analysis. Usually, retinal detachments begin at the point of fibrovascular attachment to the vascularised retina and then advance both towards the anterior and the posterior edges;

- stage 5: total retinal detachment, generally tractional and usually funnel-shaped, being sometimes exudative; according to the funnel configuration, it can be subdivided depending if the anterior and posterior portions are open or narrowed.(1,2)

As more than one stage may be present in the same eye, staging the ROP for the eye as a whole is determined according to the most severe stage present (3).

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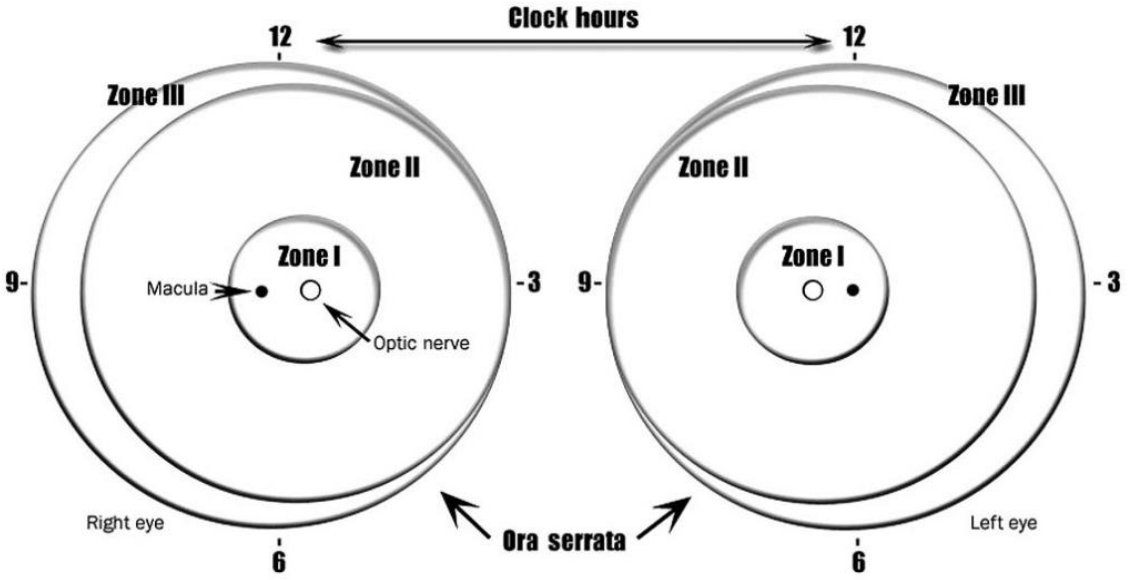


Graphic 1. Reference zones used for ROP classification (*www.eophta.com*)

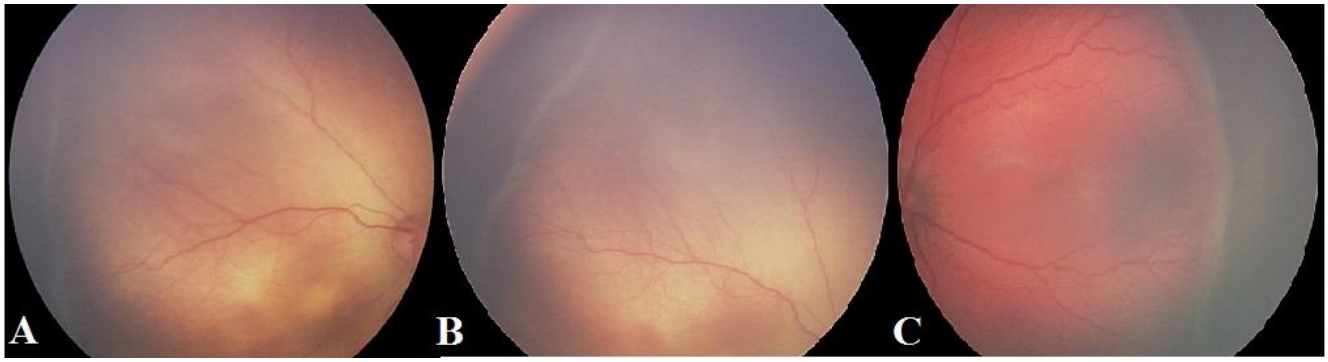


Figure 1. A. - ROP stage 1, B. - ROP stage 2, C, - ROP stage 3+ (*www.intechopen.com*)

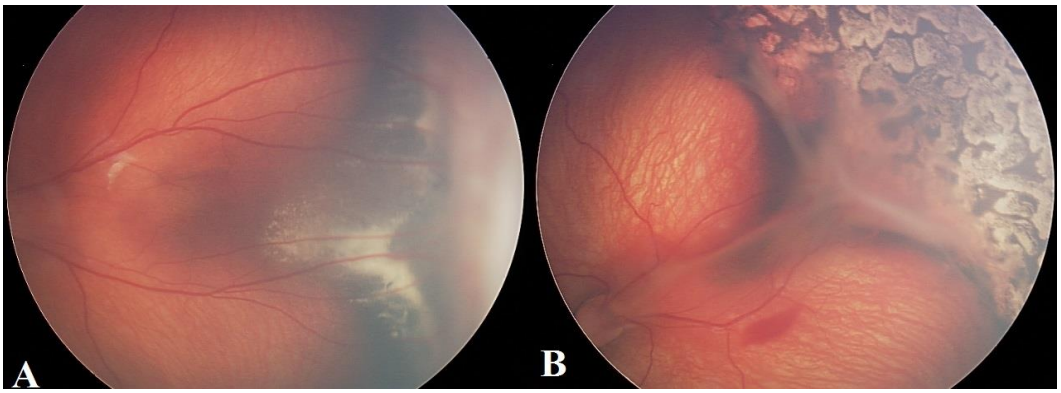


Figure 2. A. - ROP stage 4A , B. - ROP stage 4B (*www.ejournalophthalmology.com*)

Besides the lesions described above, ROP may be characterised by additional signs of disease development, called "plus-disease" (PD) factors, which include increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels which can increase in severity to include iris vascular engorgement, poor pupillary dilatation (pupillary rigidity), and vitreous haze. A "plus" sign is added to the disease stage when more than one of the above signs of severity is identified (3).

Aggressive posterior retinopathy of prematurity

The gravity ROP in zone 1 and the different aspect of severe disease in this area have required recent definition by the international committee composed of ROP classification, the concept of aggressive posterior retinopathy of prematurity. This is a severe form of ROP, which is progressing rapidly and has the characteristics: posterior location (zone I or posterior zone II), the gravity factor as opposed to the addition of poorly defined peripheral retinopathy (a system of new blood vessels, with hard features said, at the junction with the avascular retina vascular). Aggressive posterior retinopathy of prematurity extends circumferentially, the vascular changes rapidly evolving and requiring emergency treatment setting. Alternatively, the disease reaches Stage 5 of the ROP (3).

Objective: Monitoring the evolution of the retinopathy of prematurity when risk factors are involved. The screening programme for the diagnosis of ROP aims at determining the optimum timing for treatment administration in prematurely-born infants which are suspected to develop severe forms of the disease, and at reducing, as much as possible, the number of examinations in children with ROP risk, as such examinations are rather unpleasant. The intervals between examinations was not fixed, it varied according to the retinopathy development stage (3).

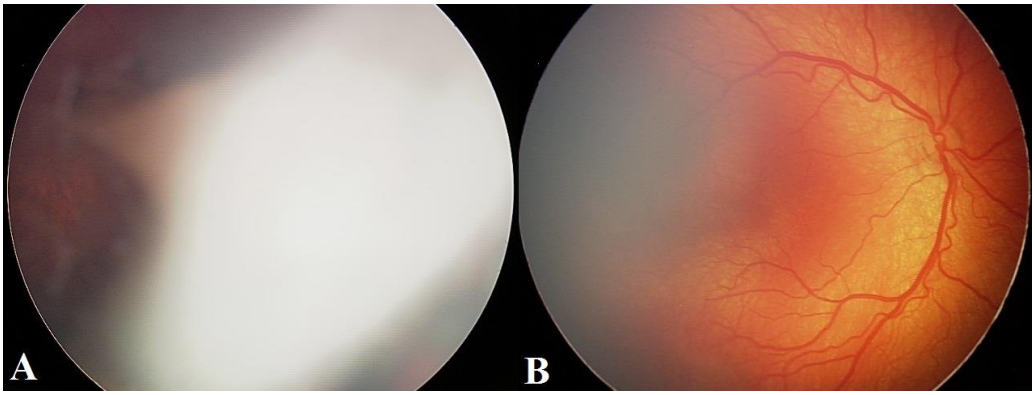


Figure 3. A. ROP stage 5, B. ROP "Plus-disease" factors (*www.retinophatyprematurity.com*)

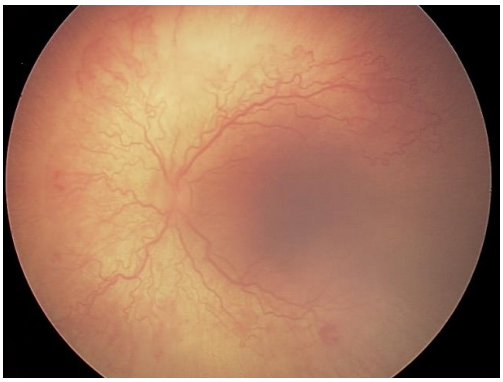


Figure 4. Aggressive posterior retinopathy of prematurity (*www.intechopen.com*)

Material and method

The research study was performed at the maternity ward in "Dumitru Popescu" Hospital Timisoara, and the research team included a neonatologist, a paediatrician and an ophthalmologist, the contribution of each team member being very important in the early screening of prematurely-born infants presenting a risk of ROP development, as well as in establishing an early diagnosis of ROP, in order to administer the optimal treatment and prevent long-term complications.

The ophthalmologist performed the examination with an ophthalmoscope. With the use of an indirect ophthalmoscope and a 20-dioptre lens, first the anterior and then the posterior poles were examined. The examination was performed according to the examination protocol included in the ROP screening.

Results

There have been examined 50 prematurely new-born infants (from Timisoara and neighboring areas) that included all the infants with BW (born weight) <1500 g and with GA (gestational age)<32 weeks and also other infants over 32 weeks that presented associated risk factors (oxygen, ventilation, sepsis, etc). The repartition on gestational age and born weight was the following: 17 infats with GA between 24-28 weeks and BW 750-1000 g, 22 infants GA 28-32 weeks and BW between 1000-1500 g,and 11 infants with GA>32 and BW>1500g.

From the study lot, 28 infants (56%) did not present ROP modification; 22 infants had ROP (44% in risk category).

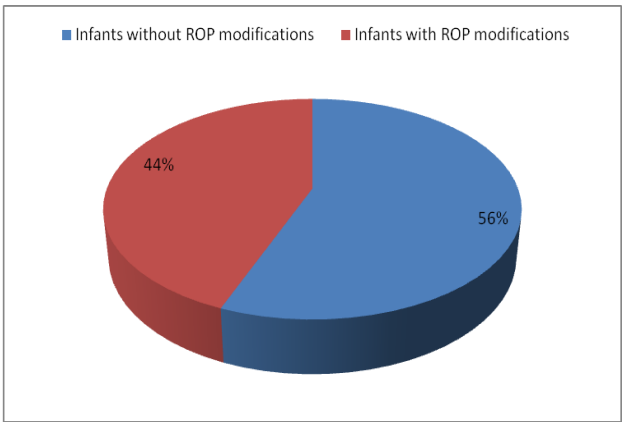
Using the ICROP classification, we have the following repartition on stage: stage 1= 10infants (18%), stage 2=7 infants (14%), stage 3=5 infants (10%), stage 4=1infants (2%), stage 5= 0 infants. All the infants examined received supplemental oxygen and most of them had anemia.

From the 6 infants (stage 3 and stage 4 of ROP), at three of them was done laser treatment.

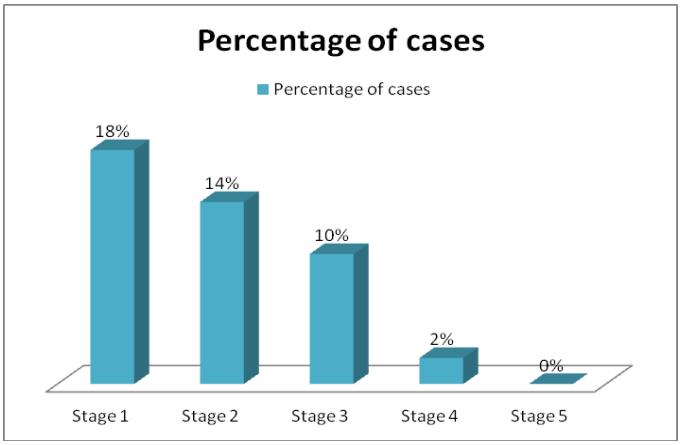
We report the different evolution of ROP in two prematurely-born infants from twins' cases, with multiple associated risk factors, admitted to the maternity ward in the "Dumitru Popescu" Hospital from Timisoara.

Case 1. The prematurely-born infant P.D. was included in the screening for retinopathy assessment at 35 weeks corrected postnatal age. The infant was diagnosed with stage-2 retinopathy of prematurity in zones I and II, with severe plus disease, and the later evolution became rapidly unfavourable. Laser therapy was performed 24 hours from the diagnosis. After the laser therapy, the evolution is still unfavourable. Approximately one month after the laser therapy, the diagnosis is stage-4 retinopathy of prematurity, and the parents were instructed to have the infant examined at a vitreous-retinal surgery clinic, yet the surgery is not performed. At present, the child is monitored at the Ophthalmology Clinic from Timisoara, with the following diagnosis: Right eye: ROP, stage 4b, partial retinal detachment, post-laser treatment status; Left eye: ROP, stage 4a, partial retinal detachment (nasal side), post-laser treatment status;

Case 2. The prematurely-born infant A.M. was included in the screening for retinopathy assessment at 37 weeks correct postnatal age. Upon ophthalmologic examination, the premature infant was diagnosed with stage-1 retinopathy of prematurity. The later development of the disease was unfavourable, and one week of monitoring, the diagnosis is posterior aggressive ROP/AO. Laser therapy was performed 24 hours from the diagnosis, and the later development was favourable. At present, the child is monitored at the Ophthalmology Clinic from Timisoara, with the following diagnosis: post-laser retinopathy of prematurity/AO, and severe myopia, and is subjected to regular assessments.



Graphic 2. The report between the infants presenting ROP modifications and the sublot without ROP



Graphic 3. Stages of ROP found in the study lot

Supplemental oxygen	50 infants (100%)
Intraventricular haemorrhage	40 infants (80%)
Respiratory distress syndrome	21 infants (42%)
Surfactant	8 infants (16%)
Sepsis	33 infants (66%)
Anaemia	49 infants (98)
Blood transfusion	3 infants (6%)
Maternal associated risk factors	18 infants (36%)

Table 1. Complications found in infants included in this study

Associated risk factors	***Prematurely P.D***	***Prematurely A.N***
Gestational age	28 weeks	29 weeks
Birth weight	1100g	1120 g
Oxygen therapy	24 h	18 h
Anemia	Hb= 6,9 g/l	Hb= 7 g/l
Blood transfusion	2	2
Intraventricular bleeding	Grad II	Grad II
Maternal risk factors	Anemia, Imminent abortion	Anemia, Placenta praevie
Apgar index	6	6

Table 2. Associated risks factors found the presented cases

Discussions

There are two theories explaining the retinopathy in premature infants: the oxygen toxicity and hypoxia theory and the "hiatus" links formation theory. Retinopathy in premature infants develops in two stages, influenced by factors such as the presence/absence of oxygen or by oxygen-independent factors (8)One major oxygen-related factor is the vascular endothelial growth factor (VEGF), together with another major oxygen-independent factor, the insulin-like growth factor 1 (IGF-1). Stage I (hyperoxia) of ROP starts with a delay in the development of retinal vascularisation immediately after birth and continues with the partial regression of existing vessels, followed by Stage II induced by hypoxia. Hyperoxia induces changes in the VEGF: suppressed VEGF in the first phase of ROP prevents physiologic retinal vascular development, while high VEGF determined by the phase-2 hypoxia of the ROP lead to abnormal vascular proliferation or neovascularisation (8,9)

A major role in this theory is played by the IGF-1 insulin-like growth factor 1, which acts directly to stimulate the VEGF for the maximum vascular development. The lack of IGF-1 in the prematurely-born infants prevents normal vascular development in phase-1 of the ROP, despite VEGF being present. As the prematurely-born infant grows, the increased IGF-1 levels in phase-2 of the ROP allow the VEGF to stimulate physiological vascular development (neovascularisation). It is believed that bringing the IGF-1 to the normal level immediately after the birth of a premature infant might be useful in preventing the ROP. At the same time, the presence of oxygen free radicals leads to the membrane alteration of the mesenchymal fusiform cells (precursors of the vascular wall), leading to the formation of "hiatus"-like links, which will prevent the formation of normal blood vessels.

The retina of prematurely born infants is not completely developed, and this is also the case of the other organs. The presence of risk factors determines an abnormal development of the retina and thus leads to the retinopathy of prematurity (9).

Various risk factors contribute to the development of ROP. They are: gestational age less than 32 weeks, and especially less than 30 weeks, birth weight under 1,500 g, and especially infants with birth weight lower than 1,200 g (1% for the infants with birth weight over 1,500 g, 80% for the infants with birth weight between 750 and 1,000 g - 10% severe forms, and approximately 100% for the infants with birth weight between 500 and 750 g - 10% develop severe forms of ROP) (10)

There is a close connection between oxygen therapy and ROP, between the duration of oxygen exposure and the severity (disease stage) of retinopathy

Hypoxia (insufficient oxygen) represents a risk factor, as the increased carbon dioxide level in the blood influences the retinal metabolism and induces extremely high VEGF, which has a negative impact on eyesight.

Assisted fertilisation methods (especially the in-vitro fertilisation) contribute to the increased incidence in ROP by increasing the incidence of multiple pregnancy and, therefore, of premature births.

Blood transfusion, as risk factor in ROP development, may be explained by the fact that premature infants receive adult haemoglobin whose oxygen desaturation index is different from the foetal haemoglobin, thus providing an additional quantity of oxygen at tissue

level. In the uterus, the tissue oxygen level is low and the normal vascular development in the retina is partially determined by the "physiological hypoxia" (10).

Vitamin E deficit occurs due to the fact that prematurely-born infants do not receive the needed vitamins in the last trimester of pregnancy. The role of vitamin E in the child development is important due to its anti-oxidant characteristics. Pharmacological doses of vitamin E have been proposed for the treatment of premature infants with low birth-weight, in order to prevent the incidence of ROP, intra-cranial haemorrhage, haemolytic anaemia and pulmonary chronic diseases. However, very high doses of vitamin E can have negative consequences, as it increases the risk of infections that can cause death. Vitamin E supplements, especially when administered intravenously, increase the risk of intra-cerebral haemorrhage. The optimal dose of vitamin E for parenteral administration to prematurely-born infants has still not yet been determined. Vitamin E is not recommended in preventing the ROP, due to its undesirable side effects, while vitamin E supplements reduce the risk of developing severe retinopathy. (10, 11)

Other possible risk factors include maternal factors (anaemia, gestational diabetes, sepsis, and antihistamine administration during pregnancy)

The risk factors associated for the two prematurely-born infants presented in this paper are mentioned in Table 2.

Increased support is given to establish the role of genetic factors in the development of the retinopathy of prematurity, a serious visual morbidity determined by premature birth. The specialty literature has reported research studies indicating the implication of three "single nucleotide polymorphisms" (SNPs), two in the CFH-gene and one in the EPAS1-gene. Upon expansion of this analysis, it was concluded that five SNPs from five genes (IHH, AGTR1, TBX5, CETP, GP1BA) are involved in the ROP development. (12)

Conclusions

Pregnant women should be monitored as closely as possible by the family physician and the obstetrician, in order to prevent premature births. A child born as closely to the term as possible has higher chances to have a well-vascularised retina, as compared with the prematurely-born infants and, therefore, there is a lower risk to develop ROP. The management of the risk factors involved in the disease etiopathogenesis and the treatment by laser photo-coagulation performed in early stages of the disease (in order to stop disease evolution before final changes occur in the retina) are important factors that contribute to less premature infants with retinopathy of prematurity.

Although both prematurely-born infants were exposed to the same associated risk factors, the evolution of retinopathy was different - the theory of the genetic factor as risk factor, contributing to the ROP development is becoming more and more plausible. Our research study was very restricted, as it included only two prematurely-born infants; therefore we cannot completely support this theory.

References

1. The International Classification of Retinopathy of Prematurity Revisited – An International Committee for the Classification of Retinopathy of Prematurity. Arch.Ophthalmol. – Vol.123, July 2005.
2. Wilkinson AR, Haines L, Head K, et al. UK retinopathy of prematurity guideline. Eye 2009;23:2137–9.
3. American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. Jan 2013;131(1):189-95
4. www.eophta.com
5. www.ejournalophthalmology.com
6. www.retinophatyprematurity.com
7. www.intechopen.com
8. Csak K, Szabo V, Szabo A, et al. Pathogenesis and genetic basis for retinopathy of prematurity. Front Biosci. Jan 1 2006;11:908-2065.Chen J., Smith LE : Retinopathy of prematurity , Angiogenesis 2007, 10(2) : 133-140
9. Fleck BW, McIntosh N. Pathogenesis of retinopathy of prematurity and possible preventive strategies. Early Hum Dev 2008;84:83–8.
10. Seiberth V, Linderkamp O. Risk factors in retinopathy of prematurity. a multivariate statistical analysis. Ophthalmologica. 2000; 214(2):131-5.
11. Karna P, Muttineni J, Angell L, et al. Retinopathy of prematurity and risk factors: a prospective cohort study. BMC Pediatr. 2005;5:18.
12. Shakir Mohamed, Kendra Schaa,Margarete e. Cooper, Elise Ahrens, Ana Alvarado, Tarah Colaizy, Mary L.Marizia, Jeffrey C. Murray, John M. Dagle: Pediatric Rerearch Vol. 65, No. 2, 2009 : Genetic Contributions to the Development of Retinopathy of Prematurity

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ETIOPATHOGENESIS AND TREATMENT OPTIONS IN SHORT BOWEL SYNDROME ASSOCIATED WITH CHRONIC LIVER DISEASE

Tepeneu NF[1,2], Daniela Chiru[1,2]

Abstract

Short bowel syndrome is a life threatening disease with a high mortality and morbidity. Since home parenteral nutrition (PN) has been established, there is an increasing number of patients surviving the acute loss of bowel function. But in the long-time these patients suffer from different complications of PN, with loss of central venous access, recurrent sepsis and finally the syndrome of progressive cholestatic ihrer disease. Both loss of central venous access and especially the progressive cholestatic liver disease are the limiting factor for the long-term survival of patients suffering from intestinal failure. Interestingly, the pathophysiologic mechanisms of parenteral nutrition induced intrahepatic cholestasis have not been solved yet and seem to be of multifactorial genesis. Cholestasis has shown to be associated with prematurity, recurrent sepsis, enteral and parenteral nutrition, especially with lipid emulsions. Enteral feeding and a well-controlled regime of parenteral nutrition lower the incidence of end-stage liver disease and, therefore, has to be optimized in the therapy of these patients.

Key words: Short bowel syndrome (SBS), parenteral nutrition (PN), liver diseases, intrahepatic cholestasis

Introduction

Short bowel syndrome (SBS) is a result of anatomic or functional loss of major parts of the small bowel, leading to intestinal failure. The estimated incidence for SBS is 24.5 (12.1-36.9) per 100000 live births, with much higher incidence in pretem babies born before 37 weeks of gestation compared with term newborns (1). A cohort study by Wales et al. showed a high mortality of SBS (6-45%)(2). On home parenteral nutrition (PN) survival rates at one and five year have been reported to be 91- 97% and 62-68% in adults and 97% and 89% in children (2).

SBS patients initially require PN and are included in an intestinal rehabilitation program, that optimises the function of the remaining bowel using medical and nutritional strategies(3,4,5).

Nevertheless, in some patients, intestinal autonomy cannot be restored and PN has to be performed for a long period of time(6).

Beside the problems with the central venous access and recurrent infections of the central venous line, the major unresolved problem remains the development of intestinal failure associated cholestasis and end-stage liver disease(7).Intestinal failure is defined as the inability of the alimentary tract to digest and absorbsufficient nutrients to maintain normal fluid balance, growth and health. Long time parenteral nutrition causes loss of venous access and recurrent catheter infections, however, the major unresolved problems of PN remains the PN associated liver disease.

After Beath et al.(8) the PN associated liver damage can be classified in three stages: early, established and late intestinal failure associated liver disease.

In an early stage there is a persistant elevation of liver enzymes, that are 1.5 times higher than normal, which persist over six weeks in infants and children. Bilirubin is <3 g/L. Liver biopsy shows steatosis in 25% of the liver parenchyma and 50% of the portal tracts show fibrotic alteration.Established liver disease is characterized by elevated liver enzymes, that are more than 1.5 times higher than normal. Bilirubin is between. 3 and 6 g/L and liver biopsy shows steatosis in more than 25% of liver parenchyma and fibrosis affecting more than 50% of portal tracts.

The late liver disease is characterized by elevated liver enzymes that are more than three times higher than normal. Bilirubin is >6 g/L. The international normalized ratio is >1,5 and additional signs for portal hypertension may be present. Liver biopsy shows fatty change with areas of intense fibrosis.

The liver damage in PN associated liver damage shows some distinct features that are different from classical liver cirrhosis. Unlike in adults, the most common histologic finding in children is intrahepatic cholestasis rather than steatosis hepatis. There is an age related histologic alteration. This may reflects the immaturity of the biliary excretion system in neonates and is related to prematurity and duration of parenteral nutrition. Compared to cholestasis in adults, in neonates it occurs early and there is a high incidence of developing progressive cholestatic liver disease (17%)(9). Complete and incomplete block of bile secretion is associated with ductular reaction accompanied by periductular fibrosis. This eventually leads to fibrous linkage of adjacent portal tracts. This stage of "biliary fibrosis" is a potentially reversible lesion(10). Biliary cirrhosis in parenteral nutrition associated liver disease is unusual, but it is the final stage characterized by portal-central fibrous septa and nodular parenchymal regeneration.

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Liver fibrosis is classified according to the criteria of Desmet et.al ranging from grade 0-4. Periportal and architectural changes form the base for grading in chronic cholestatic liver disease: grade 1: portal changes; grade 2: periportal changes; grade 3: septal changes; grade 4: cirrhotic stage(10).

Progressive cholestatic liver disease remains the most problematic life threatening complication of parenteral nutrition in short bowel syndrome. The incidence in childhood is as high as 40-60%(11,12). Potential liver damaging factors are: underlying disease, lack of enteral feeding, duration of parenteral nutrition, prematurity, extrahepatic biliary obstruction, recurrent sepsis, hypercaloric parenteral nutrition, lipid substitution > 1 g /kg body weight/day.

It is under discussion whether there is correlation between the incidence of liver disease in SBS and the underlying disease. Several studies showed a higher prevalence of liver disease in SBS compared to other causes of intestinal failure(9,11,12). It has been suggested that liver disease is less frequently associated with medical causes of intestinal failure than with surgical causes except for such cases with protracted diarrhea that show a very aggressive form of intestinal failure. In surgical SBS the length of the bowel influences significantly the development of chronic liver failure, but that is potentially dependent on the possibility of enteral nutrition. It is evident that in patients with a surgical SBS a history of multiple surgical interventions and septic periods negatively influences the prognosis. But on the long term, underlying diseases that make PN difficult to control such as diseases of protracted diarrhea show the tendency of developing PN associated liver disease more quickly.

Another important factor is the lack of enteral feeding, which is directly associated with the intensity of parenteral feeding. Total PN reduces the secretion of several gastrointestinal hormones, such as gastrin, motilin, pancreatic polypeptide, insulinotropic polypeptide and glucagon. The lower level of these hormones may lead to a reduction of motility and increases bacterial overgrowth and promotes biliary stasis (13). Therefore, it is very difficult to differentiate whether the increased risk of liver dysfunction is caused by the absence of enteral stimulation or the effects of PN. But generally enteral feeding has some important protective aspects that work without the influence of PN. It also has been suggested that the mucosal atrophy induced by the lack of enteral nutrition allows increased bacterial translocation across the gut mucosal barrier, but the results of clinical studies did not show evidence for that fact (14,15).

In addition, the absence of enteral nutrition could lead to a reduction of enterohepatic circulation and accumulation of toxic bile acids with subsequent cholestasis(16).

One of the first risk factors detected for parenteral-nutrition associated cholestasis is the relation between prematurity and liver damage. In infants with a birth weight below 1000 g the incidence for cholestatic liver disease increases substantially. Beate et al. detected a incidence of liver damage as high as 50% in infants with weight <1000 g and only 10% in infants >1500 g (17). Regarding the histology in neonates intrahepatic cholestasis is more common than steatosis hepatis, maybe reflecting the immaturity of the biliary excretion system in neonates and its susceptibility to hypoxia. It is also known that the bile salt pool in premature infants is reduced. There is a diminished hepatic uptake and synthesis of bile salts and additional a reduced enterohepatic circulation compared to infants and children(18). The development of cholestasis in infants is closely related to the duration of total parenteral nutrition (TPN). The overall incidence of cholestasis in infants on TPN is around 23% but increases up to 80% after 60 days and 90 % after 3 months respectively(17).

Recurrent sepsis is an important risk factor to develop intrahepatic cholestasis. Sepsis in

SBS is associated with bacterial overgrowth due to intestinal stasis. There is some evidence that the liver damage is caused by bacterial overgrowth leading to bacterial translocation, with consecutive sepsis, but is also an effect of bacterial endotoxins. The pathway leading to liver damage in recurrent sepsis is not disclosed yet, even so cytokines such as TNF-α are suspected to play an important role(19).

Another problem possibly related to bacterial overgrowth is the frequently observed developement of gastrointestinal ulcerations. These ulcerations within the small bowel might impair the intestinal barrier function of the bowel mucosa. There is evidence for the fact that bacterial overgrowth reduces the normal peristalsis, worsening the situation of the bacterial overgrowth(20).

Severe protein malnutrition can be responsible for developing hepatic steatosis. Proteins are needed to synthesize very low density lipoprotein (VLDL), that is needed for the triacylglycerol (TAG) export. Patient under PN should generally be substituted sufficiently with amino acids for VLDL synthesis. Up to now, the deficiency of several methionine metabolites such as carnitin, choline, and taurine has been suggested to be responsible for steatosis and cholestasis. This is important in preterm infants, since normally methionine can be converted into these metabolites by hepatic transulfuration, a metabolic pathway that is underdeveloped in these patients(21). Carnitine, cholin and taurine generally are not part of parenteral formulation and there is strong evidence that levels are, low in small patients depending on PN(22,23). Excess calories from glucose >8-12 mg/kg body weight (BW)/day are associated with hepatic steatosis, because total glucose potentially exceeds the maximum glucose oxidation rate(24). Generally high glucose infusion rates stimulate insulin release. High plasma insulin concentrations stimulate hepatic lipogenesis and the production of acylglycerol that goes along with inhibition of mitochondrial fatty oxidation. This process results in the accumulation of TAG within the hepatocytes. This could explain why continous PN infusion has a higher risk for liver damage than cyclic infusion. A period of 8 hours and more without PN a day has shown to lower the risk for liver damage(25). The incidence of steatosis hepatis is reduced when parts of the glucose energy supply is replaced by

parenteral lipid infusions. A very high parenteral lipid intake has also shown to result in hepatic complications(25).

A fat overload syndrome results in exceeded lipid administration, because of the inability to clear that amount of phospholipids and polyunsatured fatty acids (PUFA). In multivariate analysis parenteral intake of soya bean based lipid emulsions >1 mg/kgBW/day has been shown to increase the risk for liver fibrosis, even so the exact pathophysiological mechanism is unresolved(26). Studies on the effect of composition of fatty acids on chronic liver disease in PN gave some conflicting results. On the one hand rats given a high proportion of omega-3 fatty acids led to increased hepatic fibrosis and reduction of PUFA content showed no significant difference PN induced liver disease(27). On the other hand, small case studies demonstrated significant benefits of children receiving higher amounts of fish-oil based omega-3 fatty acids(28) .

Patients with SBS often have a history of multiple surgical interventions. Any kind of extrahepatic obstruction has to be avoided, since it is well-known that especially infants with extrahepatic atresia of the bile duct develop irreversible liver damage within a few weeks of age. In neonates and infants every kind of extrahepatic obstruction may worsen the prognosis for PN induced liver disease. In older patients there is a high risk for developing biliary sludge and gallstones.

Therapeutic goals in patients with SBS and liver disease

Bacterial overgrowth

In patients having problems with the enteral feeding, despite a sufficient bowel length, endoscopy can help to set the diagnosis of chronic bacterial overgrowth. Typically ulcerations in the small bowel appear, while the big bowel mucosa has a regular endoscopic and histological appearance.Often the significance of the bacterial overgrowth is not completely understood by the treating physicians. The culture of stool rarely shows pathogenic alterations in those patients. In those patients with typical ulcerations diagnosed by endoscopy an eradication therapy with a large variety of antibiotics can be attempted. As a first line non-resorbable antibiotics, such as paromomycin and vancomycin as a mono therapy can be administered. Some patients have a cycle of eradication therapy of one week every month. Additional antibiotics like metronidazole or cephalosporine derivates are sometimes helpful; in some patients a combination therapy is mandatory. On the long term some patients develop bacterial overload with resistant bacteria. In those cases eradication has to be performed, according to the culture and antibiotic testing, as a life threatening problem can develop.

Enteral feeding

One of the key points in the management is the maximizing enteral nutrition. The general question is what kind of diet should be administered and what could be the ideal amount. Hyperosmolaric diet leads to intractable diarrhea in short bowel syndrome. Dilated gut or bacterial overgrowth increased permeability can lead to allergic reaction to any protein in the formula.

Several hypoallergenic formulas exist; the most frequently used are the protein hydrolysate formulas such as Pregomine® (Milupa, Friedrichsdorf, Germany) or Alfare® (Nestle, Vevy, Switzerland). The proteins in this category are hydrolyzed and have very low allergenicity. To minimize the potential risk for food allergy, it is possible to use an amino acid formula such as Neocate® (Pfrimmer Nutritia Germany, Erlangen, Germany), Concentrations of the nutrient agent and the amount of enteral nutrition have to be adapted slowly over weeks until a bowel movement frequency of 5-8 stool/day. In patients who do not tolerate sequential feeding, it may be necessary to start continuous feeding via feeding pump. When the infants get older, the diet remains the same, but it is possible to give them some additional food. Which kind is tolerated best is not predictable. Generally the children prefer salty food, due to the high loss of electrolytes in SBS. Nutrition rich in carbohydrates always has the risk of developing lactate acidosis, but it is possible to allow patients carbohydrates and sugar in a moderate amount. It is important to start with a nutrition rich in fibers, especially in patients with a preserved colon. In addition to the general ability to absorb short-chain fatty acids derived from bacterial fermentation, patients with SBS show an adaptation to the colonic mucosa too. The significant increase of brush border enzymes in the colonic mucosa allows the active transport of peptides too and potentially a transport of carbohydrates. To increase the enteral caloric intake, the supplementation of the regular food with medium chain triglycerides (MCT) can be tried, but often patients show severe diarrheaalter supplementation with MCT oil. The optimal nutrition cannot be recommended for all patients but has to be tried in every patient. One goal in enteral feeding is to achieve a stool frequency that should not exceed five bowel movements/day.

Adjustment to parenteral nutrition

Since most of the patients receiving home parenteral nutrition continue to eat, it is necessary to estimate enteral energy absorption and to adapt the parenteral energy substitution in patients with SBS and PN. The US and UK guidelines suggest a total daily energy intake of 105-146 kJ/kg BW and a protein intake of 0.8-1.5 g/kg BW(29).

The doses and type of parenteral lipid infusion seem to be of great importance. In patients without enteral caloric intake, parenteral lipid infusion is necessary to prevent fatty acid deficiency.

US guidelines suggest that parenteral lipid infusion should supply 20-30% total energy and daily intake should be <2.5 g/kg BW and ideally <1.5 g/kg BW, according to the clinical guidelines of the National Institute for Health and Care Excellence (NICE) 2006. Most authors prefer a low-dose lipid regime with a daily intake of 1 g/kg BW and less. In patients with signs of progressive cholestatic liver disease, the lipid intake is reduced to one week with 1 g/kg BW and lipid dissolved vitamins are substituted. This regime has to be performed over a period longer than eight weeks.

Generally soya bean-based lipid intake is avoided, since the potential toxicity has been shown. Alternatives to the soya bean lipid infusions are lipid emulsions containing a mixture of long-chain and medium-chain TAG (e.g. Lipofundin®; B Braun, Melsungen,

Germany) emulsions with a high mono unsaturated fatty acids content (Clinoleic®; Baxter,Maurepas, France) and emulsions containing fish oil (SMOF Lipid; Fresenius Kabi, Bad Homburg, Germany).

Cyclic parenteral nutrition

Continuous PN showed to aggravate liver dysfunction. A cyclic parenteral nutrition seems to improve liver function and reduce insulin levels(25).The recommended 8-hour interruption is not always possible in practice. But in infants and small kids it is advisable to start with a 5-hour interruption of parenteral nutrition. Beside liver function, the cycled PN allows greater patient freedom with patients going to the kindergarten and school and, therefore, it is an important point to improve quality of life of our small patients and their parents(25).

Pharmacological treatment

Ursodeoxycholic-Acid (UDCA) is a naturally occurring hydrophilic bile acid formed in liver and intestines. It stimulates biliary flow, reduces cholesterol absorption and hepatic cholesterol synthesis. In neonates it has been shown to reduce duration of PN induced cholestasis and to improve liver function. The recommended dose in orally administered UDCA is 10 mg/kg BW(30). Some studies, however, show a rebound cholestasis after withdrawal of UDCA(31). In older patients the beneficial effect seem to be less evident and the side effects are more common, especially diarrhea(32).

Surgical options

Since Bianchi (33) established the longitudinal intestinal lengthening and tapering (LILT) for the first time in 1980,several centres presented their series(34). LILT has become a serious option for patients with SBS and their adaptation reaction, such as increasing the bowel diameter. Kim et al. (35) presented in 2003 a less difficult and faster to perform surgical procedure in order to increase bowel length and to reduce the diameter of the dilated bowel: the technique of serial transversal enteroplasty. Both techniques allow to wean patients with SBS from parenteral feeding(36). Therefore, they play a crucial role in the treatment of SBS, in form of gastrointestinal rehabilitation(37). LILT means dividing the entire bowel longitudinally along the antimesenteric and mesenteric border between the mesenteric vessels passing to each hemisegment. With this technique maximal tailoring and lengthening can be achieved. The hemisegments are reconstructed to new bowel loops around the half of the original diameter in an isoperistaltic manner. The bowel continuity is completed by anastomosis to the duodenum and colon. The longitudinal sutures can be performed by hand or stapler suture. The serial transverse enteroplasty (STEP) procedure is a easier surgical technique to perform. STEP means the serial transverse applications of a stapler from opposite directions, to create a zig-zag channel. Main advantage of this technique is that no anastomosis has to be done and that there is a much lower risk of ischemic complications compared to the LILT.

Several other techniques have been performed until now but only these two techniques have proven to be beneficial for the patients in larger series. Regarding the surviving time of patients with SBS, the patients undergoing autologous gastrointestinal reconstruction seem to have a much more favourable outcome compared to the patients who did not undergo LILT. Some series have a long-term follow-up, lasting over 80 months, with a survival rate of 77%(36). Most of the patients were able to participate in normal social life, that means they went regularly to kindergarten or school. The most significant parameter for the prognosis after LILT has been shown to be the possibility to get weaned from parenteral nutrition. Beside the bowel length, the presence of the major part of the large bowel has been shown to be significant too. Up to now the decision upon which technique has to be used depends an the center of treatment. Anyway, STEP can be performed in patients after intestinal lengthening (STEP or LILT) as a second step operation, when adaptation leads to a new dilatation of the short bowel. LILT leads to a more effective lengthening compared to STEP, but it is technically more difficult to perform, with a higher risk of complications. LILT is, therefore, performed as first choice treatment only in those patients with a very short bowel and a significant dilation. STEP technique can be performed after LILT and a secondary dilation of the bowel(34,36,37).

Intestinal transplantation

Due to the difficulties of graft rejection, the intestinal transplantation has been unsuccessful until the 1990s, when first clinical series were reported. Now there are over 60 centers worldwide that perform intestinal transplantation, with over 1 200 proceduresperformed so far(38). At the beginning intestinal transplantation was develop ed to rescue patients with intestinal failure having life threatening complications from PN.

Nowadays, patients with intestinal failure due to SBS should be referred for intestinal transplantation before irreversible liver damage develops. In patients with irreversible liver damage a combined intestine/liver transplantation has to be performed. The criteria used to determine when combined transplantation is suggested are not clearly defined yet. The functional outcome of the transplanted patients shows that 70-80% of patients who undergo successful transplantation can be completely weaned from PN(38). The major problem of intestinal transplantation remains the acute and chronic rejection and immunosuppressive therapy. Acute cellular rejection can occur at any time, but is most common in the first year. Acute rejection is the leading cause of graft loss and happens in up to 79% of all patients. Infections in intestinal transplanted patients are also common, since immunosuppression is very intensive in these patients. Especially viral infections such as Cytomegalovirus have been a major problem. Secondary malignancies to the posttransplant lymphoproliferative disorder are described in 7% of all transplanted patients. The overall outcome of all patients after intestinal transplantation has been improved

dramatically in the last 10 years. The one year patient survival now is over 80%(38).

Prognosis of intestinal failure associated liver disease

Generally progressive cholestatic liver disease is considered to be irreversible beyond the early stages of cholestasis, particularly in the presence of any degree of fibrosis in the liver. But only very few data are published about the outcome of non-cirrhotic liver injury. Patients with already morphologic liver damage, such as higher degree liver fibrosis, experience functional and biochemical liver recovery, even if the perioperative risk for patients with high grade liver fibrosis is significant elevated. The liver function improvement appears to parallel autologous gastrointestinal reconstruction and a significant improvement of enteral feeding. Histological follow-up after autologous gastrointestinal reconstruction has not been performed yet.

None of the different studies allows any comment on the possibility of histological recovery of the liver if enteral autonomy remains sustained in the long term. Older data suggest that in the presence of established fibrosis in the liver, some ultrastructüral changes persist even if biochemical recovery occurs(39).

The results from different transplantation centers suggest that enteral autonomy from PN, accompanied by a program to reduce risk factors for liver dysfunction, may allow the possibility of liver function biochemical recovery(40).

References

1. Wales PW, de Silva N, Kirn J, Lecce L, To T, Moore A.Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. J Pediatr Surg 2004;39:690-5.
2. Wales PW, de Silva N, Kim JH, Lecce L, Sandhu A, Moore AM. Neonatal short bowel syndrome: a cohort study. J Pediatr Stirg 2005;40:755-62.
3. Howard L, Ament M, Fleming CR, Shike M, Steiger E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. Gastroenterology 1995;109:355- 65.
4. Messing B, L8mann M, Landais P, Gouttebel MC, Gerard-Boncompain M, Saudin F et al Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology 1995;108:1005-10.
5. Pironi L, Paganelli F, Lahate AM, Merli C, Guidetti C, Spinucci G et al. Safety and efficacy of home parenteral nutrition for chronic intestinal failure: a 16-year experience at a single centre. Dig Liver Dis 2003;35:314-24
6. Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition treated patients: 20 years of experience at the Mayo Clinic. Mayo Clin Proc 1999;74:217-22
7. Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. J Pediatr Gastroenterol Nutr 2004;38:250-69..
8. Beath S, Pironi L, Gabe S, Horslen S, Sudan D, Mazeriegos G et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation 2008;85:1378-84.
9. Sondheimer JM, Asturias E, Cadnapaphornchai M. Infection and cholestasis in neonates with intestinal resection and long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 1998;27:131-7. -
10. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19.1513-20.
11. Buchman A. Total parenteral nutrition-associated liver disease. JPEN J Parenter Enteral Nutr 2002;26(5 Supp1):543-8.
12. Buchman AL, Iyer K, Fryer J. Parenteral nutrition-associated liver disease and the rote for isolated intestine and intestine/liver transplantation. Hepatology 2006;43:9-19.
13. 13. Greenberg GR, Wolman SL, Christofides ND, Bloom SR, Jeejeebhoy KN. Effect of total parenteral nutrition on gut hormone release in humans. Gastroenterology 1981;80(5 pt 1):988-93.
14. Alpers DH. Enteral feeding and gut atrophy. Curr Opin Clin Nutr Metab Care 2002;5:679-83.
15. Sedman PC, MacFie J, Palmer MD, Mitchell CJ, Sagar FM, Preoperative total parenteral nutrition is not associated with mucosal atrophy or bacterial translocation in humans. Br J Surg 1995;82:1663-7.
16. Gupta GL, Beath SV, Kelly DA, Millar AJ, Booth IW. Current issues in the management of intestinal failure. Arch Dis Child 2006;91:259-64.
17. Beate EF, Nelson RM, Bucciarelli RL, Donnelly WH, Eitzman DV. Intrahepatic cholestasis associated with parenteral nutrition in premature infants. Pediatrics 1979;64:342-7
18. Watkins JB, Szczepanik P, Gould J13, Klein P, Lester R. Bile satt metabolism in the human premature infant. Preliminary observations of pool size and synthesis rate following prenatal administration of dexamethasone and phenoharbital. Gastroenterology 1975;69: 706-13.
19. Jones A, Selby PJ, Viner. C, Hohbs S, Gore ME, McElwain TJ. Tumour necrosis factor, cholestatic jaundice, and chronic liver disease. Gut 1990;31:938-9.
20. Eiichi A. Miyasaka, Pamela I. Brown,Daniel H. Teitelbaum. Redilation of bowel after intestinal lengthening procedures—an indicator for poor outcome; J.Ped. Surg. 2011;46:145-9
21. Vina J, Vento M, Garcia-Sala F, Puertes IR, Gasc6 E, Sastre J et at L-cysteine and glutathione metabolism are impaired in premature infants due to cystathionase deficiency. Am J Clin Nutr 1995;61:1067-9.
22. Buchman AL. Choline deficiency during parenteral nutrition in humans. Nutr Clin Pract 2003;18:353-8.

23. Vinton NE, Laidlaw SA, Ament ME, Kopple JD. Taurine concentrations in plasma, blood cells, and urine of children undergoing long-term total parenteral nutrition, Pediatr Res 1987;21:399-403.
24. Zaman N, Tarn YK, Jewell LD, Coutts RT. Effects of intravenous lipid as a source of energy in parenteral nutrition associated hepatic dysfunction and lidocaine elimination: a study using isolated rat liver perfusion. Biopharm Drug Dispos 1997;18:803-19.
25. Hwang TL, Lue MC, Chen LL. Early use of cyclic TPN prevents further deterioration of liver functions for the TPN patients with impaired liver function. Hepatogastroenterology 2000;47:1347-50.
26. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Amt Intern Med 2000;132: 525-32.
27. Kohl M, Wedel T, Entenmann A, Stuttmann J, Bendiks M, Loff S et at. Influence of different intravenous lipid emulsions on hepatobiliary dysfunction in a rabbit model. J Pediatr Gastroenterol Nutr 2007;44:237-44.
28. Diamond IR, Sterescu A, Pencharz PB, Kim JH, Wales PW. Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 2009;48:209-15.
29. Buchuran AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003;124:1111-34
30. Chen CY, Tsao PN, Chen HL, Chou HC, lisieh WS, Chang M11. Ursodeoxycholic acid (UDCA) therapy in very-low-birth-weight infants with parenteral nutritionassociated cholestasis. J Pediatr 2004;145:317-21..
31. De Marco G, Sorclino D, Bruzzese E, Di Caro S, Mambretti D, Tramontano A et at Early treatment with ursodeoxychotic acid for cholestasis in children on parenteral nutrition because of primary intestinal failure. Aliment Pharmacol Ther 2006;24:387-94
32. Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. Gastroenterology 2003;124:1651-61.
33. Bianchi A. Intestinal loop lengthening--a technique for increasing small intestinal length. J Pediatr Surg 1980;15:145-5
34. Batra A,Beattie R.M. Management of short bowel syndrome in infancy. Selected Proceedings of Neonatal Update 2013;89-11:899-904
35. Kim HB, Lee PW, Garca J, Duggan C, Fauza D, Jaksic T. Serial transverse enteroplasry for short bowel syndrome: a case report. J Pediatr Surg 2003;38:881-5.
36. Reinshagen K, Kabs C, Wirth H, Hable N, Brade J, Zahn K et ca. Long-terrn outcome in patients with short bowel syndrome after longitudinal intestinal lengtheningand tailoring. J Pediatr Gastroenterol Nutr 2008;47:573-8.
37. Bianchi A. From the cradle to enteral autonomy: the role of autologous gastrointestinal reconstruction. Gastroenterology 2006;130(2 Suppl 1):5138-46.
38. Intestinal Transplant Registry (Homepage). Available at: www.intestinaltransplantorg
39. Dahms BB, Halpin TC Jr. Serial liver biopsies in parenteral nutrition-associated cholestasis of early infancy. Gastroenterology 1981;81:136-44.
40. Iyer KR, Horsten 5, Torres C, Vanderhoof JA, Langnas AN. Functional liver recovery parallels autologous gut salvage in short bowel syndrome. J Pediatr Surg 2004;39:340-4.

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DUPLICATED COLLECTING SYSTEM-DIAGNOSTIC AND THERAPEUTIC ASPECTS

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Abstract

Objectives: We present the clinical and imaging exploration of four patients that have duplicated collecting system emphasizing the diagnostic and therapeutic features. Methods: The cases of: Lacramioara, 10 years old- both sides duplication of renal pelvis and calyces, Alexandra 7 years old - duplicity of renal pelvis and calyces on left side, Denis 1 month old and Bianca 1 year old - complete unilateral duplicated collecting system. Results: Presenting reasons: recurrent urinary tract infections, urinary incontinence, bronchopneumonia and sepsis in the neonate. Using the ultrasound investigation, urinary tract abnormalities are being seen and then confirmed by MRI. Therapeutic attitudes differ depending on the severity of the malformation. For the 7 years old girl, the urinary incontinence is due to aberrant implantation of the megaureter in the urethra. In the case ofthe newborn patient, surgical correction has been performed later on, at the age of 2 years and a half, due to the parent's noncompliance to treatment.Conclusions: Higher ureteral dilatation along with large ureter pole is the most specific ultrasound sign for complete double urinary collecting system. Corrective surgery in these cases is necessary.

Keywords: double collector system, renal imaging

Introduction

Duplicated collecting systems, which is also known as duplex collecting systems, consists of two pyelocaliceal systems that are associated with a single ureter or with double ureters. The two ureters empty separately into the bladder or fuse to form a single ureteral orifice. (1) In the literature certain terms are used to better describe the anatomy of this duplicated collecting system, as follows:

- Duplex kidney has a single renal parenchyma that is drained by 2 pyelocaliceal systems.
- Upper or lower pole represent one component of a duplex kidney.
- Duplex system: the kidney has 2 pyelocaliceal systems and is associated with a single ureter or with a bifid ureter (a partial duplication) or, in the case of a complete duplication, with 2 ureters (double ureters) that drain separately into the urinary bladder.
- Bifid system: two pyelocaliceal systems join at the ureteropelvic junction (bifid pelvis), or 2 ureters join before draining into the urinary bladder (bifid ureters).
- Double ureters: two ureters open separately into the renal pelvis superiorly and drain separately into the bladder or genital tract.
- Upper and lower pole ureters: upper and lower pole ureters drain a duplex kidney's upper and lower poles, respectively. (2)

Duplicated collecting system is found unilateral, as well as bilateral and for most of the times, genitourinary anomalies are associated. Because in some cases this anomaly is asymptomatic, duplicated collecting system is discovered incidentally when performing imaging studies for some other reasons. Furthermore, vesico-uretheral reflux of the lower pole ureter and the upper pole ureter dilatation can be associated, as well as the presence of the Ureterocel. (3)

Concerning the imaging studies that can certificate the presence of the duplicated collecting system, abdominal ultrasonography is among the first one being used. The fact that it's noninvasive gives it great advantage when applied to children, but still needs to be followed by MRI and CT scanning for more proper investigation. (4)

Case report

The first patient that the authors present is a 10 year old girl, Lacramioara that has been hospitalized for recurrent urinary tract infections with E coli in the Nephrology department of the Clinical Emergency Hospital for Children "Louis Turcanu", Timisoara. After an ultrasonography and cystography has been performed, a right ureterocel was suspected. The MRI discovers a bilateral duplicated collecting system and the patient remains under medical observation. (Fig. 1)

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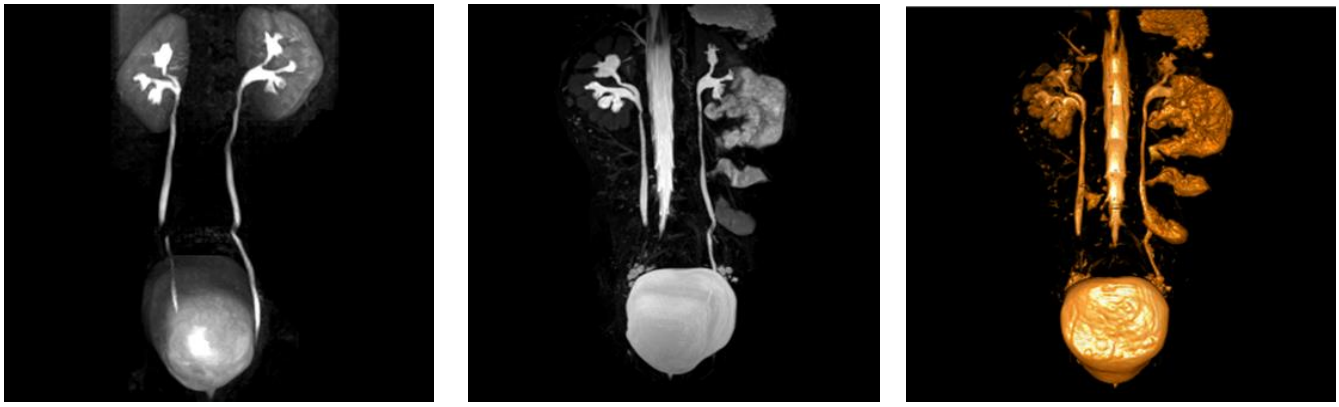

Fig. 1 MRI:bilateral duplicated collecting system (Lacramioara, 10 years old)

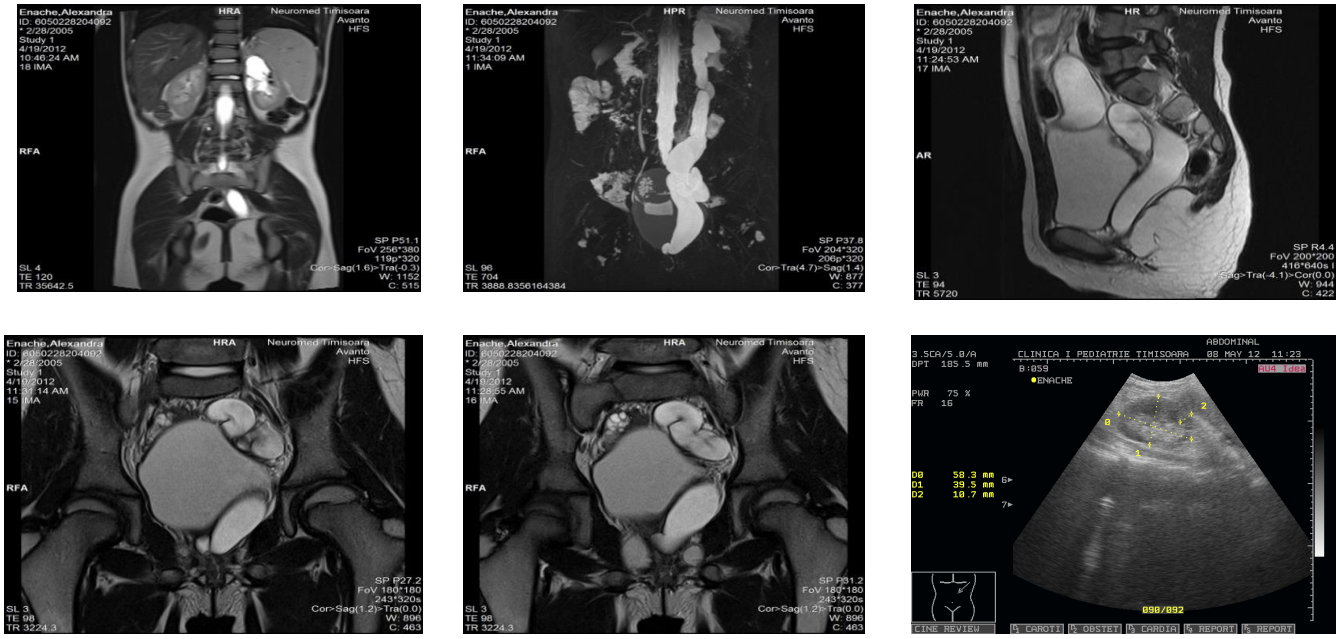

Fig.2 MRI: duplicated collecting system on the left side and the implantation of the megaureter in the urethra (Alexandra, 7 years old)

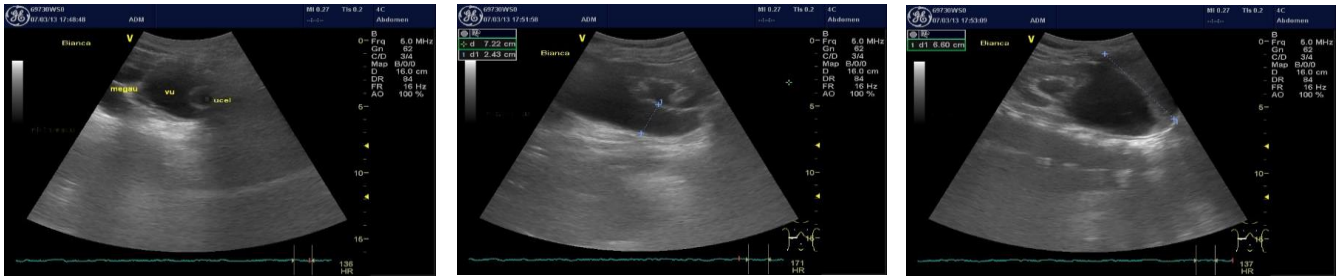

Fig.3 Abdominal ultrasound: left ureterocel (Bianca, 1 year old)

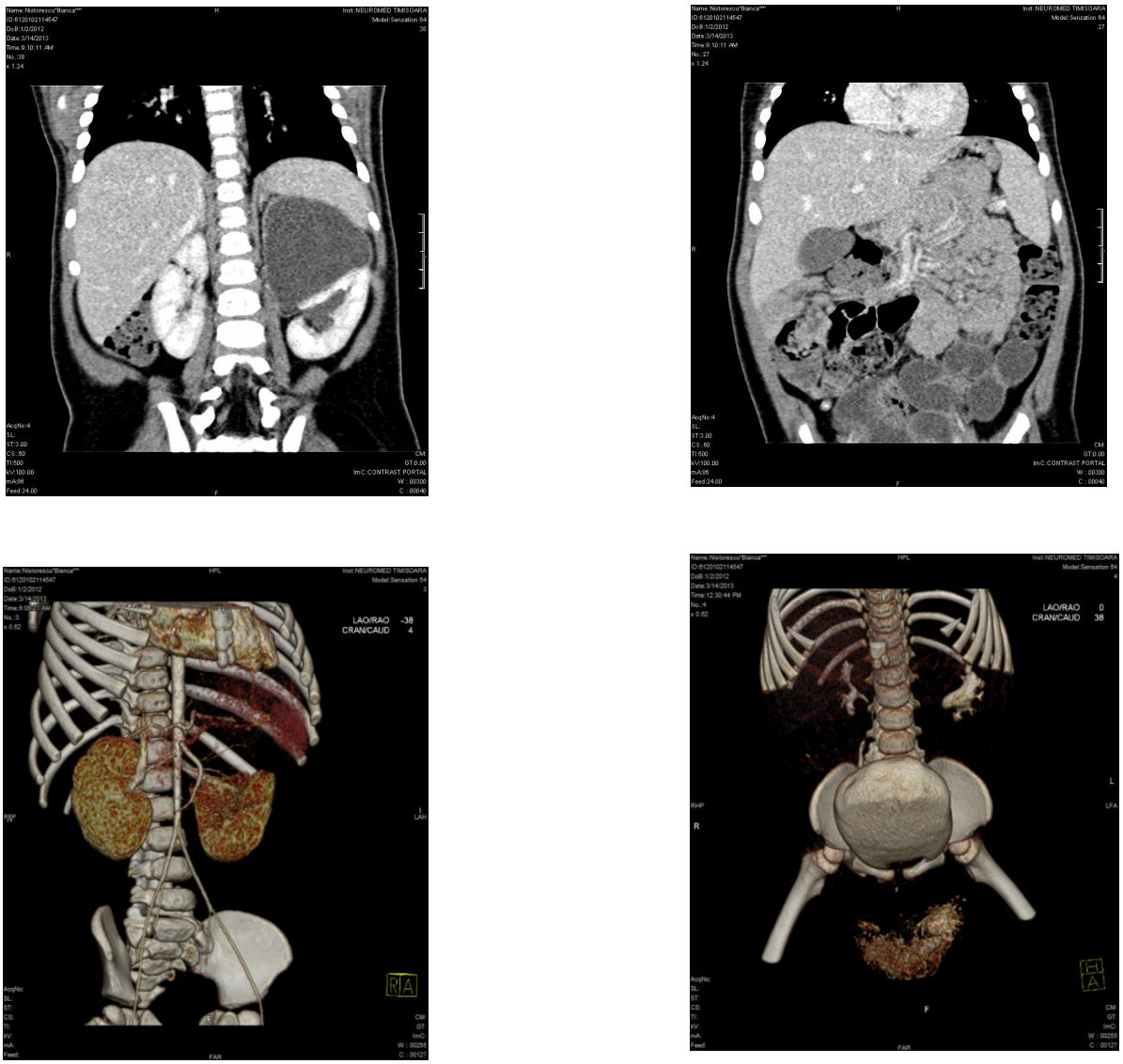

Fig.4 MRI: left duplicated collecting system (Bianca, 1 year old)

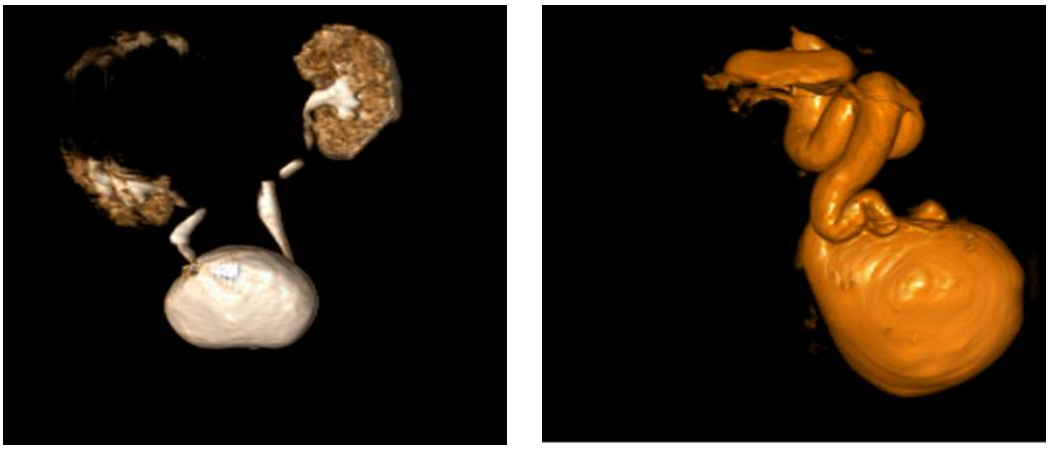

Fig.5 MRI: right duplicated collecting system (Denis, 1 month old)

The second case that of the 7 year old girl, named Alexandra, the presenting reasons are enuresis and diurnal urinary incontinence. Here as well, the MRI certificates the presence of the duplicated collecting system on the left side and the implantation of the megaureter in the urethra. Surgical correction is being performed, with the dissection and extirpation of the upper pole and of the megaureter. (Fig.2)

The third patient is a 1 year old girl, Bianca that is known from intrauterine life with a renal malformation and comes in the hospital for a bronchopneumonia. Later on, she presents for oliguria and palpebral edema, which has started a month before the actual hospitalization. She is treated with antibiotics for acute pyelonephritis, having a good outcome. Using the abdominal ultrasound, followed by a CT scan, left duplicated collecting system is diagnosed. On a further investigation, meaning a cystography, a left uereterocel is depicted, along with left megaureter and left hydronephrozis. Giving the facts, surgical correction is performed. (Fig. 3 and 4)

Our last case, a one month old baby boy, Denis, presents with sepsis and his personal history reveals repeated urinary tract infections. He is also known with hydronephrosisand megaureterfrom the neonate period. A complete right duplication is diagnosed at the MRI study. Due to his parent's noncompliance to the treatment, the anomaly has been eventually surgically corrected at the age of 2 years and a half. (Fig. 5)

Discussions

Giving the fact that duplicated collecting system is part of the reno urinary malformations that can be associated with other genitourinary anomalies, and also concerning the fact that patients do address to the doctor for numerous different reasons, we would like to emphasize the importance of ultrasonography in the screening of this anomaly. But although the ultrasonography gives us significant data about the reno urinary anatomy, its reduced sensibility cannot differentiate bifid renal pelvis from complete two ureters and that is also the case when speaking about a duplex kidney and other renal masses.(5)

On the other hand, CT scanning can help to determine if there is any obstruction and very useful in assessing the renal parenchyma. CT scanning can also be used to determine if the insertion of the duplex ureter is intravesical or extravesical. It is quite clear that CT scanning is superior to ultrasonography for diagnosing duplicated collecting system and much more helpful if we are talking about a poor renal function or even an absent one.(6)

An MRI is indicated when the extravesical insertion of an ectopic ureter is in view or whenever an upper pole is suspected. Being a complex imaging study, the costs are likewise and we should have this aspect in view when thinking about performing MRI.(7)

Once the duplicated collecting system is depicted, it only remains to adjust a proper therapeutic approach.(8) In the cases that we addressed in this article, some of the patients needed surgical correction, when others remained under close medical observation.

Conclusions

The fact that a higher ureteral dilatation along with large ureter pole is the most specific ultrasound sign for complete duplicated urinary collecting system, corrective surgery in these cases is necessary.

References

1. Dalla Palma L, Bazzocchi M, Cressa C, et al. Radiological anatomy of the kidney revisited. Br J Radiol. Sep 1990;63(753):680-90
2. Glassberg KI, Braren V, Duckett JW, et al. Suggested terminology for duplex systems, ectopic ureters and ureteroceles. J Urol. Dec 1984;132(6):1153-4
3. Bruno D, Delvecchio FC, Preminger GM. Successful management of lower-pole moiety ureteropelvic junction obstruction in a partially duplicated collecting system using minimally invasive retrograde endoscopic techniques. J Endourol. Nov 2000;14(9):727-30
4. Avni FE, Nicaise N, Hall M, et al. The role of MR imaging for the assessment of complicated duplex kidneys in children: preliminary report. Pediatr Radiol. Apr 2001;31(4):215-23. Yanagisawa N, Yajima M, Takahara T, et al. Diagnostic magnetic resonance-urography in an infant girl with an ectopic ureter associated with a poorly functioning segment of a duplicated collecting system. Int J Urol. May 1997;4(3):314-7
5. Blair D, Rigsby C, Rosenfield AT. The nubbin sign on computed tomography and sonography. Urol Radiol. 1987;9(3):149-51
6. Friedland GW. Large cloisons simulating duplex kidneys on CT. AJR Am J Roentgenol. May 1992;158(5):1171-2.
7. Jain KA. Ectopic vaginal insertion of an obstructed duplicated ureter in an adult female: demonstration by magnetic resonance imaging. Clin Imaging. Jan-Feb 2007;31(1):54-6.
8. Stec AA, Baradaran N, Gearhart JP. Congenital renal anomalies in patients with classic bladder exstrophy. Urology. Jan 2012;79(1):207-9.

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EXTRAPERITONEAL CEREBROSPINAL FLUID PSEUDOCYST FORMATION FOLLOWING VENTRICULOPERITONEAL SHUNT

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Abstract

Hydrocephalus is the most frequently treated pathology in pediatric neurosurgery and ventriculoperitoneal (VP) shunting represents the standard of treatment for this condition. Several complications have been associated with VP shunting, such as shunt occlusion, fracture and disconnection, infection, overdrainage, shunt penetration into abdominal organs, and intraperitoneal abscess formation. We report the case of a 6 month old infant with an intra-abdominal cerebrospinal fluid (CSF) pseudocyst formation secondary to VP shunting. Prior to the development of a palpable abdominal mass which would help set suspicion of an intra-abdominal shunt complication, the patient presented general, nonspecific symptoms for a period of a few days. The intra-abdominal collection was confirmed by CT-scan and we were able to successfully treat it surgically. This kind of complication is one of the rarest following VP shunting and should be kept in mind in all children who underwent the procedure and later on present with abdominal symptoms, even in the absence of an abdominal mass.

Key words: Hydrocephalus, Ventriculoperitoneal Shunt, abdominal cerebrospinal fluid pseudocyst.

Introduction

The technique of using the peritoneal cavity for cerebrospinal fluid (CSF) absorption in Ventriculoperitoneal Shunting (VPS) was developed by Kausch in 1908 (1). VPS represents the most common form of treatment for hydrocephalus, which itself is the most frequently treated condition in pediatric neurosurgery (2). It is estimated that 25–35% of patients who undergo the surgery experience at least one complication the year following the procedure. Lifetime risk of complication increases to 70-80% (1).

Most of the complications associated with VPS procedures include: shunt occlusion (accounts for up to 50% of shunt failures); shunt fracture and disconnection; infection (reported incidence of 1– 41%, average incidence of 10 – 15%); overdrainage (seen in 10% – 12% of patients and leading to complications such as slit ventricle syndrome, orthostatic hypotension, subdural fluid collections, craniosynostosis, ventricular compartmentalization, and cerebellar tonsillar herniation); and seizures (2).

The case we present is particularly interesting because the development of an abdominal cerebrospinal fluid (CSF) pseudocyst is uncommon, being encountered in < 1% of VPSs (5).

Case report

A 6 month old male infant with occipital myelomeningocele and associated hydrocephalus for which he underwent a VPS procedure at birth, was referred to our surgical unit with a 3 day history of an enlarging abdominal mass. A week earlier, the child was admitted to the Pediatric ward in a septic state, presenting fever, agitation and refusal to eat. Improvement in the patient's condition was registered during the first days of hospital stay, though he remained febrile. The development of an abdominal mass was noticed on the 5th day of hospitalization. The mass exhibited an accelerated growth rate – from being barely palpable the first day, to reaching, on ultrasound, 8 x 10 cm the second day and 8 x 14 cm the third day (at which point it occupied the entire lower abdominal floor). This, together with a worsening in the patient's condition back to the septic state presented upon admission, has led to a surgical consult being sought, and the child was transferred into our unit.

CT scan demonstrated a fluid-filled cystic mass (9.4 x 7.1 x 9 cm) with thin enhancing walls, located in the right iliac fossa (Fig. 1). An emergency exploratory laparotomy was performed and the peritoneal cyst was drained externally (about 300 ml of clear fluid was aspirated). The tip of the peritoneal catheter was found to lie within the mass (Fig. 2). The VPS was separated from the pseudocyst and the shunt was repositioned inside the peritoneal cavity, away from the lesion (Fig. 3). The patient had a favorable recovery for a period of two weeks following the procedure, which lead to discontinuation of antibiotic treatment. However, the reappearance of fever and an increase in inflammatory markers raised suspicion of a VPS infection, such that about four weeks after the initial exploratory laparotomy, a complete shunt revision was carried out. Following this, the patient's condition improved.

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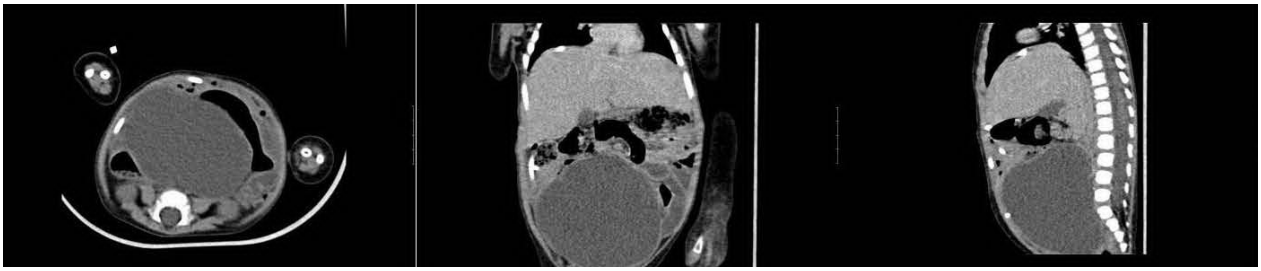

Fig. 1. Contrast enhanced CT scan of abdomen showing a large well-defined, water-density cystic mass with

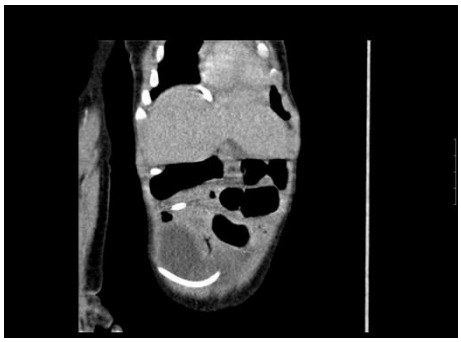

Fig. 2. Contrast enhanced CT scan of abdomen showing the tip of the peritoneal within the mass

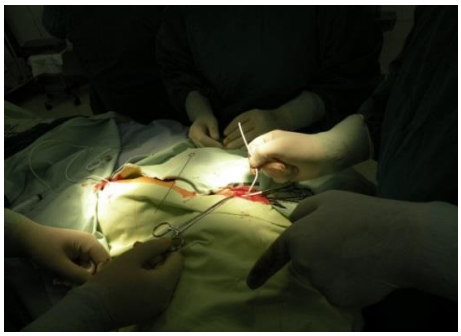

Fig. 3. Operative photograph showing the intraperitoneal repositioning of the shunt

Discussion

Uncommon VPS complications include subphrenic abscess; small-bowel perforation and formation of a CSF-enteric fistula; intractable CSF ascites; and migration of the shunt tip to locations such as the lateral ventricle, mediastinum, chest, gastrointestinal tract, bladder, vagina, and scrotum (4, 5).

Abdominal CSF pseudocyst development is a rare complication of VPS (< 1% of cases) (3). Most commonly, the timeframe from the shunting procedure to pseudocyst formation ranges from 3 weeks to 5 years (6). Patients with abdominal CSF pseudocyst usually present with abdominal symptoms (6); these symptoms generally precede the signs of shunt malfunction, which often makes it difficult to correlate the patients' symptoms with the presence of the VPS, thus leading to a delay in diagnosis (7). This description fits the case of our patient, who was admitted for abdominal symptoms and only displayed signs of shunt malfunctions after 5 days of hospital stay. In our patient, symptoms upon hospital admission were nonspecific and most of them pointed out solely to a VPS infection and not to the development of a CSF pseudocyst.

As employed in this case, both ultrasound and CT scan can be used in determining the diagnosis – ultrasound typically demonstrates a well-defined lucent mass with posterior acoustic enhancement, while CT scan usually reveals a cyst containing homogenous water-density fluid (8). CT scan is, however, the imaging of choice, because it provides accurate localization of the cyst (9). However, none of the imagistic modalities can accurately provide a definitive diagnostic; moreover, in the presence of sepsis, none can distinguish between infected and noninfected cysts. Percutaneous aspiration/drainage of the pseudocyst can also be employed as a means of diagnosis; however, if infection is present, as it was in our patient, the pseudocyst should be excised and the shunt tube should be removed (8).

The direct cause that led to the formation of our patient's CSF pseudocyst is unknown. Several causes can be considered. As reported by Hahn et al., infection is the most prominent cause of pseudocyst formation (accounting for 80% of cases) and should be presumed as the cause of all abdominal pseudocysts, until proven otherwise (1). When there is an infection, the usual intra-abdominal response is peritoneal catheter sheathing; CSF draining into the sheaths can then lead to the development of CSF pseudocysts (1). Other factors that predispose to pseudocyst formation are peritoneal adhesions from a previous surgery; previous shunt revisions; increased CSF proteins; malabsorption of CSF due to conditions such as subclinical peritonitis; and an allergic reaction to the peritoneal catheter or to a CSF component (8). Of no less importance is the quality of the

shunt itself – VPSs used in hospitals from countries with small health budgets are often made of materials that retain some antigenic proprieties and can be rejected by the human body.

Overall, CSF pseudocyst formation represents a poor prognostic sign as far as the future viability of using the peritoneal cavity for shunting goes. Once a patient developed a CSF pseudocyst, it is increasingly likely that the condition will recur or that the peritoneum will suffer an inability to properly absorb the CSF (1).

Conclusion

In spite of complications, VPS remains the method of choice for the long-term relief of increased intracranial pressure. Though uncommon, abdominal CSF pseudocyst formation should be kept in mind in all children who underwent a VPS surgery and present with abdominal symptoms, even in the absence of an abdominal mass. Clinicians managing patients with VPSs must be familiar with their possible complications, such that early recognition and prompt treatment can be implemented.

References

1. Chung JJ, Yu JS, Kim JH, Nam SJ, Kim MJ. Intraabdominal Complications Secondary to Ventriculoperitoneal Shunts: CT Findings and Review of the Literature. AJR Am J Roentgenol. 2009;193:1311-7.
2. Weprin BE, Swift DM. Complications of Ventricular Shunts. Techniques in Neurosurgery. 2002;7:224–242.
3. Kim HB, Raghavendran K, Kleinhaus S. Management of an abdominal cerebrospinal fluid pseudocyst using laparoscopic techniques. Surg Laparosc Endosc. 1995;5:151-4.
4. Agha FP, Amendola MA, Shirazi KK, et al. Unusual abdominal complications of ventriculoperitoneal shunts. Radiology. 1983;146:323-326.
5. Agarwal T, Pandey S, Niranjan A, Jain V, Mishra S, Agarwal V. Unusual complication of ventriculoperitoneal shunt surgery. Journal of Pediatric Neurosciences. 2009;4:122-123.
6. Ersahin Y, Mutluer S, Tekeli G. Abdominal cerebrospinal fluid pseudocysts. Childs Nerv Syst. 1996;12:755-758.
7. Yamashita K, Yonekawa Y, Kawano T, Ihara I, Taki W, Kobayashi A, Handa Y, Kaku Y. Intra-abdominal Cyst Following Revision of Ventriculoperitoneal Shunt. Neurol Med Chir (Tokyo). 1990;30:748-52.
8. Gupta P, Ghole V, Eshaghi N. Abdominal CSF pseudocyst. Applied Radiology. 2009;38: 29-30.
9. Sharma AK, Pandey AK, Diyora BD, Mamidanna R, Sayal PP, Ingale HA. Abdominal CSF pseudocyst in a pateint with ventriculo- peritoneal shunt. Indian Journal of Surgery. 2004;66: 360-363.

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INGESTION OF MAGNETS: CASE REPORT

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AbstractAbstract

Foreign body ingestion is a very common topic among pediatric surgeons due to the nature of their patients. Magnets ingestion is rare and it is a certain etiologic factor for gut wall ischemia or ileus leading to serious life threatening complications. In this case report we present a 3 year old boy that swallowed multiple magnetic balls. We managed to retrieve the objects by using minimal incision and by avoiding opening the GI tract wall. We consider magnetic body ingestion a surgical urgency and differential diagnosis with other type of items is essential to further care.

Key words: foreign body ingestion, magnets.

Introduction

Foreign body ingestion is a very common problem in pediatrics. The severity of the problem depends on the nature of the swallowed object. Ingestion of a magnet is expected to follow the behavior of the most of the ingested foreign bodies, but ingestion of more magnets is well-known that it can bring up serious problems like intestinal ischemia followed by perforation. The aim of this case report is to present a case of multiple magnet balls ingestion and the surgical method we used for their extraction.

Case report

A 3 year old boy presented in our department with nausea, vomiting and abdominal pain for approximately 24 hours. The physical examination showed spontaneous pain in the epigastric region, emphasized by local palpation, without tenderness or acute abdomen signs. The X-ray of the abdomen didn't show any signs of ileus or other organic abnormalities but it presented multiple radio-opaque round-shaped objects in the stomach (see Picture 1). The objects had the aspect of a "bunch of grapes" with a small loop of interconnected balls detaching from the ball, giving a highly suggestive image of multiple magnetic bodies ingestion. We have made the decision to intervene early in order to extract the items. The first attempt was to pull out the magnets using the endoscopic approach, but it failed, so we reoriented over the open surgical approach. Minimal median incision in the epigastrium was performed and the stomach and first part of the duodenum have been exposed. Intraoperative palpation of the stomach and duodenum presented a bunch of hard balls strongly connected one to other. We decided to model the ball of magnets into a linear string of magnetic balls so a 14 Ch Nelaton tube inserted through the esophagus connected to the aspiration device could retrieve the balls (see Picture 2). The intraoperative X-Ray that followed the removal of the balls showed up two more restant magnetic balls in the first part of duodenum that we pushed back in the stomach by gently squeezing the gut wall. We used the same method to retrieve the last two items. The method was successful and we managed to avoid opening the GI tract. After intervention the patient had an eventful evolution being discharged after 4 days.

Discussion

Foreign body ingestion is a very common problem in children, due to their natural cognitive development. [1] The peak of incidence of foreign body ingestion is between 6 months and 3 years old and in most of the cases (80-90%) and more than 70% of the cases involves children younger than 6 years. [2, 3]. Spontaneous passage through the GI tract occurs after the foreign body gets into the small bowel. [2] Most of the objects removed from the aero-digestive tract of the children (50-80%) are represented by food items like seeds, grains or pieces of meat and 30% of the non-food items are represented especially by coins, but screws, pins or button batteries were also reported. [5] Button batteries ingestion is well known for its complication due to local mucosal burning that can extent even to perforation. [6] Magnets ingestion is rare, but it can cause important damage to the GI tract regarding their size or shape. Single magnet ingestion is usually harmless and it behaves like most of the foreign bodies in the GI tract. Multiple magnet ingestion is way more rare - 20 cases of multiple magnet ingestion in children in the United States between 2003 and 2006 [8] - and in can produce serious complications. The magnets tend to produce ischemia, pressure necrosis, perforation, fistula formation or intestinal obstruction by holding the intestinal wall in between them. [1,6] Between 2003 and 2006 in a statistic resume of Consumer Product Safety Commission in the United States, it is reported one death by the complications of multiple magnet ingestion.

Most of the children present acute abdomen signs or intestinal obstruction or other symptoms 1 to 7 days after the ingestion, but there were reported cases where signs or symptoms were absent. [9] The universal principle of foreign body ingestion that considers every object that passes the esophagus able to pass the whole GI and be spontaneous eliminated is not applicable in multiple magnet ingestion. [1]

Early investigations like X-Rays of the abdomen and pelvis in magnet ingestion is indicated to detect the number of the objects and surgical intervention is the key to prevent or to reduce complications. [10] When the history is not concluding, multiple radio-opaque findings should alarm the physician into excluding multiple magnet ingestion. [2].

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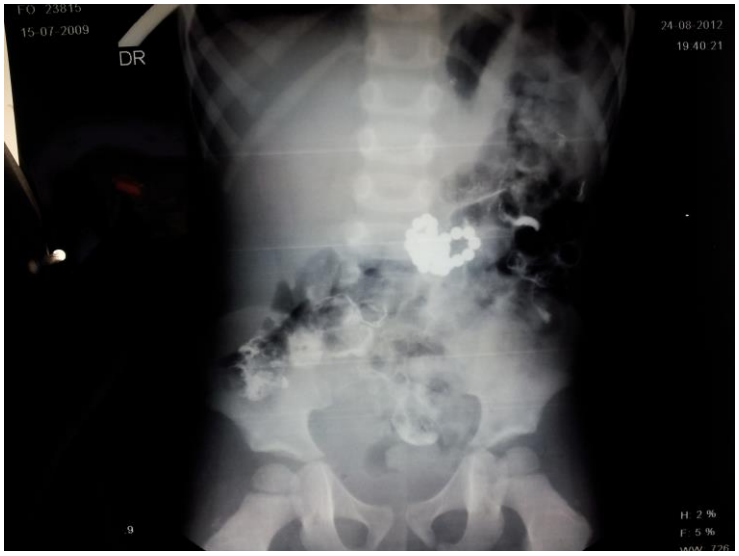
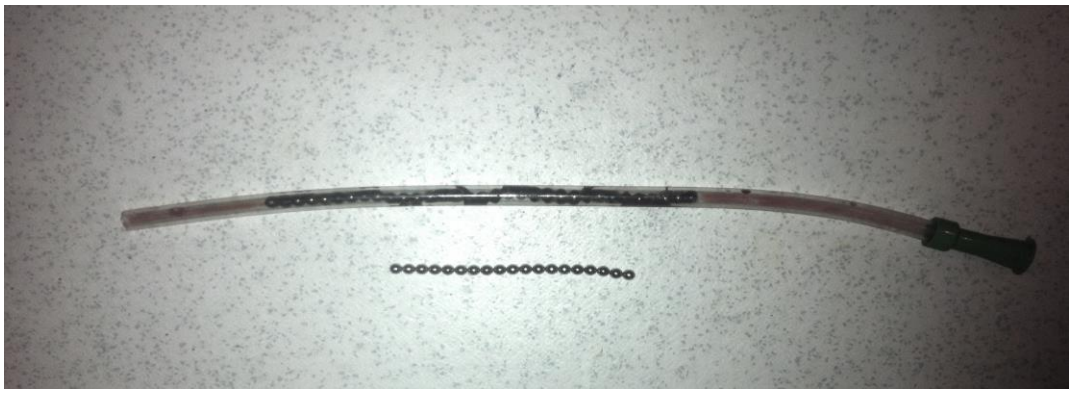


Picture 1. Abdomen X-Ray findings of multiple magnet ingestion



Picture 2. The Nelaton tube with string-shaped magnets

Picture 3. Magnetic balls puzzle

In case of a single magnet ingestion is confirmed it is recommended to simply follow-up the patient by simple physical examinations until the object is expelled. Some authors recommend counseling the patient not to wear clothes with metallic parts (like buttons, belts, chains or buckles) due to the attraction that can be produced between the inside item and the abdominal wall. [11] A large literature review made by Naji H [1] presents the explorative laparotomy as the elected intervention for retrieving the magnets (42 cases), followed by laparoscopy (5 cases) – two of them being in converted into laparotomy. Endoscopy is reported in only one case as the only way of extraction the foreign body from the GI tract, but it's known as an auxiliary procedure in 4 cases. One case was reported when the magnetic objects passed the GI tract without any interventionMost of the magnetic objects are found in toys (see Picture 3) and ingestion is often associated with other metallic objects and most of the children have underlying psychosocial, psychiatric and developmental risk factors. Clinicians have the duty to aware the parents of the risks represented by multiple magnet ingestions and other metallic objects. [1, 11]

Conclusion

Foreign body ingestion is very frequently among toddlers and young children. Most of the times it doesn't represent a surgical challenge due to the capacity of the GI tract to adapt and eliminate the objects, but sometimes – depending on the nature or number of the items – surgical intervention is recommended as an urgency in order to prevent life-threatening complications. Multiple magnetic ingestion can lead to mechanical ileus or peritonitis (due to perforation) and it always need to be excluded by abdominal X-Ray findings. In order to avoid complications, early surgical intervention is strongly indicated to remove the objects and depending where the foreign bodies are located different approaches should be considered. In our case, minimal incision keeping the gut wall intact was possible for the extraction of multiple magnetic balls from the stomach and duodenum.

References

1. Naji H, Isacson D, Jan F, et al. Bowel injuries causted by ingestion of multiple magnets in children: a growing hazar. Pediatr Surg Int (2012) 28:367–374.
2. Uchida K, Otake K, Iwata T, et al. Ingestion of multiple magnets: hazardous foreign body in children. Pediatr Radiol (2006) 36: 263–264.
3. Uyemura MC. Foreign body ingestion in children. Am Fam Physician. 2005 Jul 15;72(2):287-291.
4. GW Holcomb III, JP Murphy, DJ Ostlie, et al. Ashcraft's Pediatric Surgery, 5th ed. Philadelphia: Elsevier Saunders, 2010
5. Puri P, Hollwarth M. Pediatric Surgery – Diagnosis and Management. Berlin: Springer-Verlag, 2009.
6. Michael L, Jacqueline M, Guarisco J, et al. Update on the Diagnosis and Treatment of Caustic Ingestion. The Ochsner Journal. 2009; 9(2): 54-59.
7. Ilce Z, Samsun H, Mammadov E. Intestinal Volvulus and Perforation Caused by Multiple Magnet Ingestion: Report of a Case. Surg Today (2007) 37:50–52
8. Biervliet V, De Putte V, De Jaegher A, et al. Multiple Magnet Ingestion : A Real Challenge for the Pediatric Surgeon. Acta Clinica Belgica 67.4 (2012): 298-300
9. Dutta S, Barzin A. Multiple Magnet Ingestion as a Source of Severe Gastrointestinal Complications Requiring Surgical Intervention. Arch Pediatr Adolesc Med. 2008; 162(2): 123-125.
10. Sahin C, Alver D, Gulcin N, et al. A rare cause of intestinal perforation: ingestion of magnet. World J Pediatr 2010;6(4):369-371.
11. Wong, Helen HL, Phillips, et al. Opposites attract: a case of magnet ingestion. CJEM : Journal of the Canadian Association of Emergency Physicians 11.5 (Sep 2009): 493-5.
12. Schieling S, Snyder SK, Custer M. Magnet Ingestion. J Pediatr 2008;152:294.

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METABOLIC BONE DISEASE OF PREMATURITY

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Abstract

The survival rate of premature infants has significantly increased during the last few decades. As a consequence, new disorders such as osteopenia of prematurity have been emerging.

Osteopenia (metabolic bone disease - MBD) is common among extremely low birth weight infants (ELBW, <1000 g birth weight) despite current practices of vitamin and mineral supplementation. (9)The diagnosis of osteopenia of prematurity is based evidence for less bone mineral density compared to fetuses or infants at the same gestational age in the absence of laboratory parameters and/or clinical signs for rachitis or other metabolic bone disease. The incidence of osteopenia among infants born before 28 weeks of gestational age are high.

The aim of this paper is to review the information regarding the prevention and treatment of osteopenia of prematurity. The latter is essential for the prevention of osteoporosis in adulthood, a significant problem of public health.

Keywords: osteopenia, prematurity, metabolic bone disease

Introduction

The survival rate of premature babies has increased significantly in recent decades through the continuous progress made in intensive care units in hospitals where resuscitation equipment is available respiratory. Among the common conditions of morbidity due to the prematurity a growing interest is focusing now on the metabolic bone disease of the prematurity , also called osteopenia of prematurity.(5)

Osteopenia, a condition characterised by a reduction in bone mineral content, is a common disease of preterm babies. Prematurely born infants are deprived of the intrauterine supply of minerals affecting bone mineralization.The aetiology is multifactorial: inadequate nutritional intake (or poor absorption) of Ca and P, insufficient intake of vitamin D, insufficient intake of protein, limitation of physical activity.

Identification of risk factors is essential for monitoring of osteopenia. Some of the risk factors include low birth weight, prematurity, chronic placental lesions, prolonged parenteral nutrition, prolonged immobilization, long term administration of drugs such as corticosteroids, methyloxanthines, furosemide, abnormalities in vitamin D metabolism, inadequate maternal intake of Ca, P.

Neonatologists, pediatricians and endocrinologists should investigate premature, low birth weight infants that have high serum alkaline phosphatase and have at least one risk factor.

Bone physiology

Amounts of minerals necessary for normal development of the skeleton are very different depending on the age of the child.

During intrauterine life, and especially in the last trimester of pregnancy occurs skeletal development. Significantly increases bone volume with gestational age and bone formation activity is due to the modeling process, an increase in trabecular thickness (trabecular thickening rate being about 240 times higher in fetal than in children).The mineralization process is determined by synthesis of the organic bone matrix by osteoblasts (osteoid) onto which calcium and phosphate salts are deposited. This process increases exponentially between 24 and 37 weeks of gestation, reaching the 80% of mineral accretion in the third trimester.(1)

At term the newborn skeleton has a high physical density (expressed as bone mass divided by bone volume). Fetal accumulation of calcium and phosphorus in the last three months of gestation is about 20 g to 10 g, which represents the storage rate of 100-120 mg/kg/day of calcium and 50-65 mg/kg/day to phosphorus. A very important role in the formation of the fetal skeleton is played by the placenta. Calcium transfer from mother to fetus through the placenta occurs through active transport of basement membrane calcium pump. Moreover, the placenta is able to convert vitamin D to 1,25-dihydrocholecalciferol which is fundamental for transferring phosphate to the foetus. The foetus is maintained hypercalcemic in a high calcitonin and estrogen environment which promotes the modelling/remodelling ratio in favour of modelling and thus increasing the endocortical bone. Such premature babies will be deprived of the intrauterine supply of calcium and phosphorus that cause bone mineralization.

Chronic impairment of the placenta may alter phosphate transport, explaining why children with intrauterine growth retardation may have osteopenia. Demineralization is observed in children born to mother chorioamniositis and placental infection.

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After birth, bone density decreases term newborns by 30% in the first 6 months of life. This is largely due to an expansion of the size of the marrow cavity, which occurs more rapidly than the increase in cross-sectional area of the bone cortex.

There are significant changes in the hormones: estrogen reducing maternal and postnatal growth of PTH levels due to a reduction in the supply of calcium from the placenta.(2)

As the serum calcium levels falls in the first day of life, PTH secretion is stimulated. During this transition the response of the parathyroid gland to falling levels of ionised calcium is blunted. This finally results in a physiological nadir in neonatal serum calcium levels within the first 48 hours of life. Of note, PTH level is still within the normal range for term babies or adult, but represents a decrease from foetal levels.

Many factors play a role in the absorption of calcium: maternal vitamin D status, the solubility and bioavailability of calcium salts, calcium quality and quantity, the amount and type of lipid and bowel function. Calcium absorption from the intestine occurs by both passive and active transport dependent on vitamin D. In a newborn preterm low mineral content of human milk associated with poor absorption from the gut determine a net reduction of calcium and phosphorus supply. Phosphorus absorption occurs in the jejunum and depends on food intake. The phosphorus supply regulates calcium absorption and retention: the higher is the phosphorus content of the diet, the higher is the calcium retention. However, an excessive amount of one decreases the absorption of the other.

Among the other pathogenic factors, also problems related to inadequate supply of calcium to babies, which require parenteral nutrition and interference of several drugs, may contribute to determine preterm osteopenia with an increasing risk of bones fractures.

Risk factors of osteopenia

a.Prematurity

Prematurity is a very important risk factor because transplacental transport of Ca and P is higher after 24 weeks of gestation. Almost 66% of fetal Ca accumulation occurs during this period.Overall, it is estimated that 80% of mineral accumulations occur in the 3rd trimesters of pregnancy. As a result, premature babies have low bone mineral deposits that rise may not be sufficient for rapid bone growth that occurs during the post-natal period.(5,9)

b.Lack of mechanical stimulation

Bone development is strongly influenced by forces that are exerted upon the bones therefore preterm infants are vulnerable due to lack of mechanical stimulation. the lack of mechanical stimulation may lead to increased bone resorption, decreased bone mass and increased urinary Ca loss . The skeletal structure remodels according to the prevalent forces, leading to increased bone strength at areas where this is most needed. Inactivity due to immobilisation (incubator) stimulate osteoclastic bone reabsorption and urinary excretion of calcium plus low muscle activity prevents the formation of new bone.(20)

c. Drugs administration

Neonatologists and other specialists should be careful in the prolonged administration of drugs. In preterm infants, the use of long term methylxanthines and diuretics such as furosemide, increase renal Ca excretion required for bony growth. Also, use of high dose systemic corticosteroids has been demonstrated to impair bony growth.

d. Other pathological conditions

Sepsis, cerebral pathology, neuromuscular disorders may result in prolonged periods of immobility associated with poor bone mineralization. In addition chronic damage to placenta may alter the phosphate transport; therefore babies with intrauterine growth restriction may be osteopenic (14). Demineralization is observed also in mother with chorioamnionitis and placental infection.

Clinical features

Most cases of MBD are evolving asymptomatic. This disease remains silent until a severe demineralisation occurs.

The most evident clinical findings of osteopenia (MBD) are deformity of the skull (diastasis of the suture, enlargement of the sagittal fontanelle and frontal bosses, craniotabe), thickening of the chondrocostal junctions and of the wrists, rib and long bones fractures. Softening and/or fractures of the ribs can cause pulmonary changes and respiratory distress, typically between 5 and 11 weeks of age.

Often, the earliest clinical features of osteopenia in neonates are these complications. High risk infants, such as VLBW infants or neonates received for long term medications such as diuretics should be regularly monitored for the possibility of osteopenia. This would allow the condition to be detected as early as possible so that appropriate management may avert the development of serious complications.

Laboratory investigations

Diagnosis of osteopenia is mainly done by serum analysis. Serum alkaline phosphatase (APS) - the single investigation - correlates poorly with bone mineral status. 90 % of APS serum bone originates. APS babies grow at all in the first 2 weeks after birth and then further increase in conditions of insufficient intake of minerals. APS values above 1000 IU / L is often associated with fractures and growth failure.(3,16)

Serum P values <2 mmol / l suggests risk MBD while values < 1.8 mmol / l is associated with radiologically evident rickets.Using serum APS and P values increases the sensitivity and specificity of the diagnosis MBD. Serum calcium is not a useful marker of bone mineral 's status as the level of calcium is maintained in the normal range on account of long bone reabsorption and may be elevated even under hypophosphatemia.(7)

Markers of nutritional status should be assessed baseline, and then weekly during the initial phase; once the newborn is stable, assessment must be done at the starting of total enteral nutrition and successively every 2–3 weeks. If MBD is diagnosed and nutritional supplementation is started, a periodic assessment of laboratory data is necessary to evaluate the response to treatment also when babies are discharged from hospital. The key clinical goal is to maintain normocalcemia and normophosphatemia and to

avoid an excessive calciuria. Once levels of APS, calcium and phosphorus normalize, serum analysis can be performed monthly up to 6 months of age and then every 3 months.(4)

More sensitive markers of bone mineralization deoxypyridinoline , pyridinoline , C - terminal propeptide of type 1 collagen - collagen metabolism intermediates and osteocalcin - a non-collagenous bone matrix protein secreted by osteoblast. However, these tests are not widely available.

ELBW premature infants have a low threshold of urinary excretion of P leading to deletions increased P and decreased serum phosphate. Tubular reabsorption of P of 95 % suggests an insufficient intake of P and is associated with hypercalciuria.

Determination of vitamin D has low sensitivity and specificity for the diagnosis BMOP and vitamin D has a role in the etiology of the disease.

Radiologic appearance depends on the severity and duration of impairment and bone mineralization radiological diagnosis is imprecise. Radiological changes of long bones are not radiographically detectable bone mineral to decrease by over 20% usually changes early, acute are hardly highlighted.

Ultrasound is a method available bone quantitative, inexpensive, simple and non-invasive assessment of bone density.(18) The sonographic studies have shown the development of bone and early after birth have demonstrated that the severity of the process, is correlated with gestational age .(19)

Dual energy X-ray absorbitometry (DEXA) is able to determine the bone mass content of neonates and can predict the risk of fractures since it is sensitive in detecting small changes in BMC and BMD. (13)Its use is now validated in neonates both term and preterm ones.DEXA reflects most accurately the state of bone mineralization in preterm infants.(14)

Profilactic treatment

To a very large extent of MBD prevention methods overlap disease therapy. Early nutritional interventions decrease the prevalence and severity of MBD.

Most infant formulas for premature infants are fortified with Ca and P in order to compensate for the deficiency of intestinal absorption (compared to human milk) and provide a surplus of Ca and P . (15) Provides fortified milk intake of Ca and P much improved and fortified breast milk feeding preterm nutrition is a safe method that results in improving weight gain and waist. In the absence of breast milk invigorator recommended premature breast milk supply and administration of calcium, phosphorus and vitamins per os.(17)

Deficits largest bone and waist were reported in infants under 1250g who experienced and intrauterine growth restriction. Enter hence the non- nutritive factors discussed role of breast milk in preventing long-term effects of MBD.

Studies have shown that bone mineralization is much better for premature infants fed preterm formula compared with infants fed standard formula (for mature newborn) demonstrating that poor dietary intake has major role in the etiology MBD.

In the case of an insufficient enteral intake (unfortified breast milk) is recommended calcium and phosphorus per os until the weights of 2.5 kg: total intake of 200 mg/kg/day calcium and 100 mg/kg/day of phosphorus. Calcium and phosphorus by preterm milk breast - fed less than 1500 g birth weight recommended by the age of 8 weeks or at least until the weight of 2000g .(8)

Fortification of human milk with fortifier containing calcium and phosphorus nutrition intervention is the best long-term results. Using the formulas for preterm nutrition is safe and effective alternative if the milk is not available or is not. If premature MBD or other obvious nutritional deficiencies (usually ELBW) is advised that breast milk fortification, supplementation or administration of preterm formulas continue until the weight of 3.5 kg or even up to the age corrected 9 months.(10,12)

If radiological evidence of rickets and enteral intake of minerals is not enough despite administration of fortified breast milk or preterm formula (usually premature NG under 800g) may be used per bone mineral supplementation: up to 40 mg/kg/day as elements up to 20 mg/kg/day elemental P. When used orally supplements of calcium and phosphorus is recommended that they not be added to milk (breast or formula) (risk of precipitation).

Orally mineral supplementation is stopped when APS is below 500 IU/day. Vitamin D is the only adjuvant therapy MBD, providing optimal nutritional intake of energy, protein and minerals are based therapy. The recommended daily dose is 400 IU/day summand vitamin D dose administered via nutritional supplement vitamin D per os. Breast milk contains 22-100 IU/liter, the amount varying according to the mother's diet, sun exposure, pigmentation and type of maternal supplementation with vitamin D. The formulas contain about 400 IU/liter. (6) There is evidence that higher doses of vitamin D are not necessary and do not influence the evolution of MBD but increases the risk of toxicity. Maximum tolerable limit for vitamin D is 1000 IU. Maternal supplementation with 4000 IU/day vitamin D increases the concentration of vitamin D in breast milk to 100 IU/l and improves bone mineralization rate of child. More studies show that the initiation of a program of early passive motion when it supports handling leads to increased bone mineralization (increased bone length, bone mass, lean body mass) and weight gain.(11)

Conclusions

1. Optimizing energy intake, protein and mineral of prematurity is the most important preventive measure and therapeutic MBD.

2. Breast milk and formula for premature babies are the best options for feeding preterm infant in the first months of life.

3. Spontaneous movements (mainly antigravity flexion and extension) are important for bone structure and mineralization in premature infants. QUS may become an important diagnostic modality for the evaluation, treatment, and follow-up of bone strength and osteopenia in this unique population.

4. Prognosis of MBD is good, short and long term if the correct nutritional intake.

5. No need for a higher intake of 400 IU vitamin D / day.

References

1. Youn Ho Shin, MD, Hye Jung Shin, MD, and Yong-Jae Lee, MD, MPH, PhD, Vitamin D status and childhood health, Korean J Pediatr. 2013 October; 56(10): 417–423.
2. Tolppanen AM, Fraser A, Fraser WD, Lawlor DA., Risk factors for variation in 25-hydroxyvitamin D_3 and D_2 concentrations and vitamin D deficiency in children, J Clin Endocrinol Metab. 2012 Apr; 97(4):1202-10.
3. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T, Trikalinos TA., Vitamin D and calcium: a systematic review of health outcomes, Evid Rep Technol Assess. 2009 Aug; (183):1-420.
4. Moreira A, February M, Geary C., Parathyroid hormone levels in neonates with suspected osteopenia, J Paediatr Child Health. 2013 Jan; 49(1):E12-6. doi: 10.1111/jpc.12052.
5. Shannon M Mitchell, Stefanie P Rogers, Penni D Hicks, Keli M Hawthorne, Bruce R Parker and Steven A Abrams, High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support, BMC Pediatrics 2009, 9:47 doi:10.1186/1471-2431-9-47.
6. Nassrin Khalesi, Seyed Mohsen Bahaeddini, Mamak Shariat, Prevalence of Maternal Vitamin D Deficiency in Neonates with Delayed Hypocalcaemia, Acta Medica Iranica 2012. 50(11):740-745.
7. Rigo J, Mohamed W.M, Curtis MDE., Disorders of calcium/phosphor/magnesium metabolism,Disease of the Fetus and Infant, Vol 2, 9th ed. Elsevier Mosby, 2011, 1523-56.
8. Czech-Kowalska J, Pludowski P, Dobrzanska A, Kryskiewicz E, Karczmarewicz E, Gruszfeld D, Pleskaczynska A, Golkowska M, Impact of vitamin D supplementation on markers of bone mineral metabolism in term infants, 2012 Oct;51(4):781-6. doi: 10.1016/j.bone.2012.06.023.
9. Viswanathan S, Khasawneh W, McNelis K, Dykstra C, Amstadt R, Super DM, Groh-Wargo S, Kumar D, Metabolic Bone Disease:: A Continued Challenge in Extremely Low Birth Weight Infants, JPEN J Parenter Enteral Nutr. 2013 Aug 20.
10. Nehra D, Carlson SJ, Fallon EM, Kalish B, Potemkin AK, Gura KM, Simpser E, Compher C, Puder M, A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for metabolic bone disease, JPEN J Parenter Enteral Nutr. 2013 Sep; 37(5):570-98. doi: 10.1177/0148607113487216.
11. Steichen JJ, Gratton TL, Tsang RC, Osteopenia of prematurity: the cause and possible treatment. J Pediatr. 1980; 96(3, pt 2):528-534.
12. O'Connor DL, Jacobs J, Hall R, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula, J Pediatr Gastroenterol Nutr. 2003;37(4):437-446.
13. Lucas-Herald A, Butler S, Mactier H, McDevitt H, Young D, Ahmed SF, Prevalence and characteristics of rib fractures in ex-preterm infants, Pediatrics. 2012 Dec; 130(6):1116-9. doi: 10.1542/peds.2012-0462.
14. Bulloch B, Schubert CJ, Brophy PD, Johnson N, Reed MH, Shapiro RA, Cause and clinical characteristics of rib fractures in infants, Pediatrics. 2000 Apr;105(4):E48.
15. Marquardt ML, Done SL, Sandrock M, Berdon WE, Feldman KW, Copper deficiency presenting as metabolic bone disease in extremely low birth weight, short-gut infants, Pediatrics. 2012 Sep;130(3):e695-8. doi: 10.1542/peds.2011-1295.
16. Tinnion RJ, Embleton ND., How to use... alkaline phosphatase in neonatology, Arch Dis Child Educ Pract Ed. 2012 Aug;97(4):157-63. doi: 10.1136/archdischild-2012-301633.
17. Hitrova S, Slancheva B, Popivanova A, Vakrilova L, Pramatarova T, Emilova Z, Yarakova N, Osteopenia of prematurity--prophylaxis, diagnostics and treatment, Akush Ginekol (Sofiia). 2012;51(7):24-30.
18. Rack B, Lochmüller EM, Janni W, Lipowsky G, Engelsberger I, Friese K, Küster H., Ultrasound for the assessment of bone quality in preterm and term infants, J Perinatol. 2012 Mar;32(3):218-26. doi: 10.1038/jp.2011.82.
19. Fewtrell MS, Loh KL, Chomtho S, Kennedy K, Hawdon J, Khakoo A.,Quantitative ultrasound (QUS): a useful tool for monitoring bone health in preterm infants?, Acta Paediatr. 2008 Dec;97(12):1625-30.
20. Eliakim A, Nemet D., Osteopenia of prematurity - the role of exercise in prevention and treatment, Pediatr Endocrinol Rev. 2005 Jun;2(4):675-82.

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PREVENTION OF NEONATAL RESPIRATORY DISTRESS SYNDROME

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Abstract

Respiratory distress syndrome (RDS) is one of the most frequent respiratory diseases and is a leading cause of neonatal morbidity and mortality. RDS is also known as hyaline membrane disease. Preterm birth is the most important risk factor in the development of respiratory distress syndrome. The maine cause of severe respiratory syndrome is lung surfactant deficiency. Inadequate surfactant production leads to diffuse alveolar atelectasis, edema, cell injury and the decrease of lung compliance.

Prenatal diagnosis to identify children at risk, prevention of disease by antenatal administration of glucocorticoids, improving perinatal and neonatal care, advances in respiratory support and surfactant administration , have reduced mortality associated with respiratory distress syndrome.

Despite recent advances in perinatal management of severe neonatal respiratory distress syndrome, controversies still exist.(1,3,9)

Keywords: neonatal respiratory distress syndrome, surfactant therapy, prevention, antenatal steroids, preterm birth

Introduction

Adequate pulmonary function is essential for the newborn survival. For this reason, lung development during perinatal period was a vast area of research. Intrauterine development of respiratory system begins from a lung bud. Then he divides, branch out and penetrate the mesenchyme, progressing to the periphery. The lung development goes through five stages:

I. Embryonic stage (5 weeks post conception)- proximal airway development
II. Pseudoglandular stage (5-16 weeks of gestation)- lower airway development
III. Canalicular stage (17-24 weeks)- vascular canals multiply to form the alveolar-capillary respiratory membrane
IV. Saccular stage (24-37 weeks)- characterised by dilatation of terminal respiratory units into alveolar saccules and ducts
V. Alveolar stage (37 weeks to 3 years postnatally)- formation of secondary alveolar septa that partition the terminal ducts and saccules into mature alveoli (4,10)

The lungs have two types of circulation. Bronchial arteries are part of systemic circulation and the pulmonary arteries participate to the pulmonary gas exchange. Proper lung function requires anatomical integrity and maturity respiratory control. In fetal life, the lung is only 10% oxygenated. It is filled with fluid, which at birth is discharged and replaced with air, to ensure and maintain residual capacity. During the labour, the compression performed on the thorax facilitates the removal of lung fluid. The intraalveolar lung fluid moves into the interstitium and is partially absorbed by the capillaries. Pulmonary surfactant coats the alveoli and lowers the surface tension, facilitating lung expansion. Respiratory distress syndrome (RDS) represent an important pulmonary pathology. It occurs mainly in premature infants, due to pulmonary immaturity and lung surfactant deficiency. (4,5,10)

Incidence

It is inversely related to gestational age:
- thus 80% at 24 weeks of gestation;
- 70% at 28 weeks of gestation;
- 25% at 32 weeks of gestation;
- 5% at 36 weeks of gestation.

Risk factors for RDS (2,11) are shown in table 1.

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Table 1. Risk factors for RDS.

Increased risk	Decreased risk
• Prematurity • Male gender • Familial predisposition • Cesarean section without labor • Perinatal asphyxia(Apgar score <4) • Chorioamnionitis • Multiple pregnancy • Matern diabetes • Early clamping of the umbilical cord • Hypothyroidism • Hypothermia • Maternal malnutrition • Non-immune hydrops fetalis	• Chronic intra-uterine stress • Prolonged rupture of membranes • Maternal hypertension or toxemia • Maternal use of narcotics/cocaine • Intrauterine growth retardation or small for gestational age • Antenatal glucocorticoids • Tocolytic agents • Hemolytic disease of the newborn • Black race

Pathophysiology

The primary cause of respiratory distress syndrome is inadequate pulmonary surfactant (production or decreased secretion). The surfactant is a lipo-protein complex secreted by the type II pneumocytes. It is found in fetal lung at 20 weeks of gestation , but in the alveoli is found much later. Surfactant is also found in the amniotic fluid at 28-32 weeks of gestation. After 34-35 weeks of gestation, the pulmonary surfactant has appropiate levels.

Surfactant has a number of properties who has the purpose to reduce surface tension and the tendency to collapse of the alveoly. This properties are: increase pulmonary compliance, alveolar stabilization and pressure drop necesary to maintain alveoli open. The structurally immature and surfactant deficient lung has low compliance and a tendency to atelectasis. Intraalveolar pressure drop, alveolar collapse, altered ventilation/perfusion ratio, intrapulmonary shunts, decreased pulmonary compliance and pulmonary resistance growth, leads to the appearance of hypoxia, hypercarbia and acidosis (figure 1).(5,11)

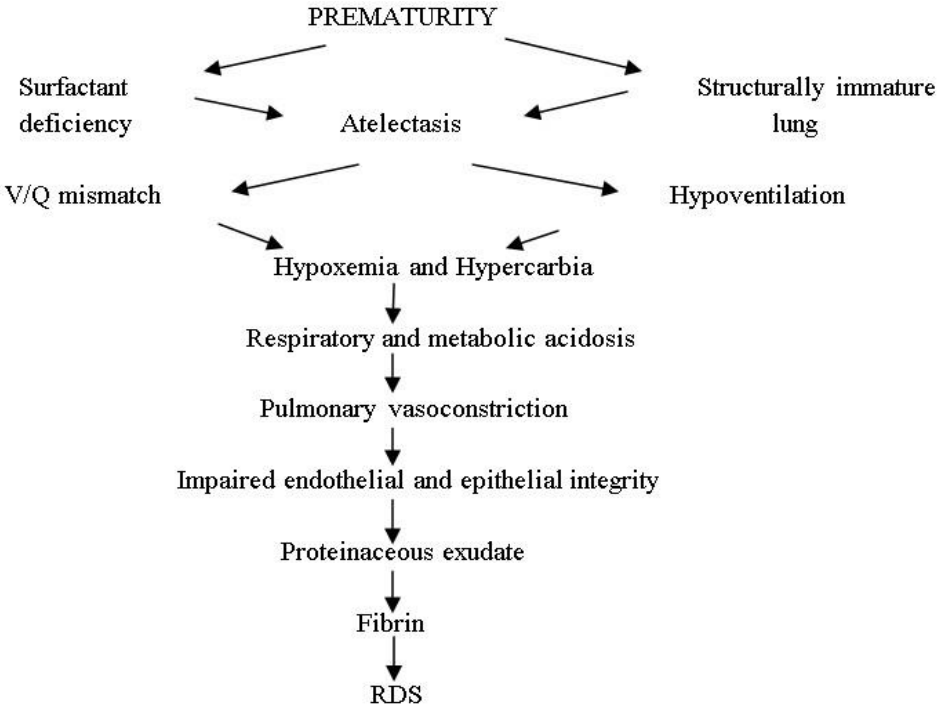

Fig. 1. Pathophysiology of RDS.

Pathological anatomy

Macroscopically the lungs appear congested, atelectatic, with a dark red color. Microscopically is seen diffuse alveolar atelectasis, pulmonary edema and dillated alveolar capillaries and lymphatics. In the alveoli is observed hyaline membrane homogeneous or granular. Amniotic cells, intraalveolar hemorrhage and interstitial emphysema are also found. Hyaline membranes rarely appear before 6-8 hours from birth. (4,5,10)

Clinical features

Signs of RDS appear immediately after birth or within 4 hours. Respiratory distress severity is assessed after Silverman Score (table 2).(2)

Table 2. Signs of RDS.

Silverman Score	**Chest movements**	**Xiphoid Retraction**	**Intercostal Retraction**	**Expiratory Grunt**	**Nasal flaring**
Score 0	Equal	None	None	None	None
Score 1	Respiratory lag	Minimal	Minimal	Audible with stethoscope	Minimal
Score 2	Seesaw respiration	Marked	Marked	Audible	Marked

Silverman Score interpretation :

- score 0 - indicates no respiratory distress
- score 4-6 – indicates moderate respiratory distress
- score 7-10 – indicates severe respiratory distress

Respiratory distress syndrome is characterized by one or more of the following: nasal flaring, chest retractions, tachypnea, grunting and cyanosis. Tachypnea represent respiratory rate over 60/min. It is due to an attempt to increase minute ventilation to compensate for a decreased tidal volume and increased dead space. Retractions occurs as the infant is forced to generate a high intrathoracic pressure to expand the poorly compliant lungs. Grunting represent the compensation mechanism against alveolar collapse. Grunting results from the partial closure of the glotis to maintain the alveolar volume. Other clinical features may includ: oliguria, hypothermia, hypotension, hypotonia and acidosis. (3,4,5,12)

Investigations

- *Antenatal:* determination of lecithin/sphingomyelin ratio in the amniotic fluid:

- normal is >2 (except newborns from diabetic mother where a ratio > 2 can mean hyaline membrane disease)
- L/S ratio ¯1,5 can signify high risk for hyaline membrane disease.

- *Postnatal:*

I. Noninvasive monitoring:

- $SaHbO_2$ – normal = 92-98%
  – < 88% indicate the need for assisted ventilation
- Transcutaneous blood gas: normal parameters PaO_2 arterial = 55-80 mmHg, $PaCO_2$ arterial = 40-50 mmHg, pH arterial = 7,30-7,40.
- Blood pressure: try to maintain systolic blood pressure > 60mmHg and/or medium blood pressure (MAP) >30 mmHg.

II. Monitoring acid-base balance and blood gases.

Initially laboratory changes are characterized by: hypoxemia, hypercarbia, acidosis (first respiratory, then metabolic or mixed – it is desired to maintain pH value between 7,30-7,40).

III. Chest x-ray highlights low lung volumes and a bilateral, reticular granular pattern with superimposed air bronchograms. In more severe cases there is complete "white out" of the lung fields.

IV. ECG exam is required to specify cardiac impairment.

V. Transfontanelar ultrasound exam – required to specify the neurological complications.

VI. Blood exam: Ht, Hb, urea, creatinine, glucose.

VII. Blood culture – for infections risk assessment.(1,2,5)

Management

The treatment purpose of child with respiratory distress syndrome is to avoid hypoxemia, acidosis, fluid overloading in an attempt to avoid hypovolemia and hypotension and also minimizing lung injury. The most important advances in prevention and treatment of respiratory distress syndrome are:

a) antenatal glucocorticoids,
b) surfactant administration,
c) continuous positive airway pressure (CPAP).

These have decreased morbidity and mortality from respiratory distress syndrome.(7,8,9)

Antenatal glucocorticoids accelerate fetal lung maturity. This process is made by increasing formation and surfactant secretion, and also maturing the lung morphologically. Prenatal steroids decrease the risk of RDS and additionally decrease the risk of intraventricular haemorrhage. Antenatal glucocorticoids are recommended in all pregnancies with threatened preterm labour below 34 weeks of gestation. Administration of corticosteroids, like betamethasone 12 mg every 24 hours, 2 doses 48 hours before birth or dexamethasone 6 mg, 4 administrations every 12 hours, 48 hours before birth, to mothers at least 24-48 hours before premature birth, decreases the incidence and

severity of the RDS. Glucocorticoids also reduces the incidence of other complications of prematurity, such as intraventricular hemorrhage, pneumothorax, patent ductus arteriosus, ulceronecrotic enterocolitis. (8,9,11)

Surfactant therapy: Exogenous natural surfactant (porcine/bovine source) or synthetic (table 3), may be used prophylactic to the preterm infant (< 32 weeks of gestation)in the delivery room in the first minutes after birth, as soon as the infant has been stabilized. The benefit of this action is to replace the surfactant before RDS develops and to avoid or ameliorate lung injury. The administration of surfactant is curative to infants who already developed RDS and require mechanical ventilation and supplemental O_2. Administration of exogenous surfactant to infants who require oxygen concentration greater than 30% and mechanical ventilation for the treatment of hyaline membrane disease improved the survival of this babies and reduced the incidence of immediate pulmonary complications (interstitial emphysema, pneumothorax). But, unfortunately, did not reduce the incidence of bronchopulmonary dysplasia. Several studies have shown that two doses, 12 hours apart, may be more effective than single dose therapy. More than 2 doses is rarely required and is rarely effective. (2,9)

Table 3. Surfactant preparations licensed in Europe in 2013.(9)

Generic name	Trade name	Source	Manufacturer	Dose(volume)
Beractant	Survanta®	bovine	Ross Laboratories (USA)	100mg/kg/dose(4ml/kg)
Bovactant	Alveofact®	bovine	Lyomark Pharma(Germany)	50mg/kc/dose (1,2ml/kg)
Poractant alfa	Curosurf®	porcine	Chiesi Farmaceutici(Italy)	100-200mg/kg/dose (1,25-2,5ml/kg)

Nasal CPAP: Invasive mechanical ventilation of an immature lung has long-term side effects and should be avoided as much as possible. Prophylactic CPAP after birth is recommended to all preterm infants with less than 30 weeks of gestation who are breathing spontaneously and no clinical criteria for intubation and mechanical ventilation, until their clinical condition can be assessed. CPAP help prevent alveolar and airway collapse.(9,11)

Mechanical ventilation: All neonates with respiratory distress syndrome should be intubated and mechanically ventilated, in order to reduce mortality. Mechanical ventilation is recommended to all preterm babies with: RDS and severe apnea who do not respond to CPAP, $PaCO_2$ >55-60 mmHg, pH <7,25, gestational age less than 27 weeks and no antenatal glucocorticoids. Duration of mechanical ventilation should be limited as much as possible, since all modes of ventilation can induce lung tissue damage.(9)

Oxygen therapy after stabilization: At preterm babies who require oxygen therapy, oxygen saturation must be maintained at values between 85-93%. Higher O_2 concentrations will increase the risk for retinopathy of prematurity, chronic lung disease, brain injury, ulceronecrotic enterocolitis. Administered oxygen must be humidified and heated, because dry and cold gas causes heat loss and airways damage.

Antibiotic therapy : Antibiotics are often started in babies with RDS, until laboratory results from blood culture arrives. A common regimen includes Ampicillin with Gentamicin, or cephalosporin with amikacin or metilmicin.(9)

Thermoregulation: Temperature control (36,5-37,5°C) is important to minimize metabolic demands and oxygen consumption. An incubator or radiant warmer must be utilized to maintain a neutral thermal environment for the infant.

Without complications respiratory distress syndrome to premature infants often get worse in 2-4 days from birth, with a slow improvement after. Some babies with RDS dies, although this is rare in the first day of life. If it occurs, is usually between 2 and 7 days. Thus,to a birth weight below 501 g survival rate is 10% and the risk of developing bronchopulmonary dysplasia is 100%. If the weight at birth is between 1001-1500 g, survival rate is approximately 96% and the risk of developing bronchopulmonary dysplasia decreases significantly.

The aim of management of RDS is to provide intervention that will maximize survival while minimizing potential adverse effects.

References

1. Cloherty J, Stark A, Eichenwald E. Manual of Neonatal Care. 7th ed. Lippincott, Wilkins and Williams; 2012.
2. COLECȚIA GHIDURI CLINICE PENTRU NEONATOLOGIE- Managementul sindromului de detresă respiratorie prin deficit de surfactant, Publicat de Asociația de Neonatologie din România, 2011.
3. Ilie C – Neonatologie – probleme de baza ale asistentei imediate si precoce a nou nascutului; ed. Balcanic, 2002.
4. Lupea I – Tratat de neonatologie, Ediția a-V-a, Editura medicală universitară IuliuHațegan, Cluj-Napoca, 2005
5. Stoicescu S: Boli pulmonare neonatale. Ed Universitara Carol Davila Bucuresti 2009
6. Kotecha S, Allen J. Oxygen therapy for infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2002;87:F11–F14
7. Hibbard J, Wilkins I, Sun L, Gregory K, Haberman S, Hoffman M, et al. Respiratory morbidity in late preterm

births. JAMA Journal of the American Medical Association. 2010;304:419–425
8. Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. American Journal of Respiratory and Critical Care Medicine.2011;184:172–179
9. Sweet D, Bevilacqua G, Carnielli V, Greisen G, Plavka R, Saugstad OD, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome. Neonatology. 2013 ;103:353-368
10. Joshi S, Kotecha S. Lung growth and development. Early Hum Dev. 2007;83:789–794
11. William H. Tooley Intensive Care Nursery at UCSF Medical Center Intensive Care Nursery House Staff Manual. 79. 2004 The Regents of the University of California. Respiratory Distress Syndrome (RDS).
12. Gomella TL, M. Cunningham. 2009. Neonatology: management, procedures, on-call problems, diseases and drugs. (6th ed), 48-67
13. Greenough A, Morley C, Roberton N. Acute respiratory diseases in the newborn. In: Roberton N editors. Textbook of Neonatology. 2nd ed. London: Churchill Livingstone; 1992;p. 385–504
14. Hany Aly, MD, FAAP*, Respiratory Disorders in the Newborn:Identification and Diagnosis Pediatrics in Review Vol.25 No.6 June 2004, pg201-207
15. Pickerd N, Kotecha S. The Pathophysiology of Respiratory Distress Syndrome. Child Health and Paediatrics. 2009;19:153–157
16. Clark R. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more.Journal of Perinatology. 2005;25:251–257
17. Levine EM, Ghai V, Barton JJ, Strom CM. Mode of delivery and risk of respiratory diseases in newborns. Obstetrics and Gynecology. 2001;97:439–442
18. Surg Cdr SS Mathai, Col U Raju, Col M Kanitkar, Management of Respiratory Distress in the Newborn, MJAFI 2007; 63 : 269-272

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SEVERE SEPIS AND INCIPIENT RENAL FAILURE IN A TYPE 1 DIABETES CHILD

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Abstract

The authors present the case of a 15-year-old girl with a brutal onset of juvenile diabetes in the context of multiple organ dysfunction syndrome (MODS). The symptoms appeared suddenly: vomiting, diarrhea, hyperthermia, dehydration symptoms. Two days after admission, were noted diabetic coma symptoms (dry skin, fruity breath odor, confusion) associated with Bullous Pemphigoid lesions on the surface of left hemibody, right basal pneumonia with both acute respiratory and kidney failure. After three weeks of intensive treatment, the evolution was slowly favourable: renal function recovering, blood sugar level stabilization and epithelialization of skin lesions.

Usually, infections may precipitate type 1 diabetes onset in children and teens. Severe infections and sepsis could be associated with high sugar levels that are stabilized as soon as infection is solved. The particularity of this case consists of permanent type 1 diabetes, although the sepsis has been solved.

Keywords: diabetes mellitus, sepsis, MODS.

Introduction

Sepsis is the systemic response to infection and is defined as the presence of SIRS (systemic inflammatory response syndrome) in addition to a documented or presumed infection.

MODS (multiple organ dysfunction syndrome) means at least two organ failure and it requires the presence of the following criteria (in the context of infection) or the patient must meet one or more of the following conditions in the last 24 hours (1,2,3):

- Cardiac: heart rate (HR) <54/min, mean arterial blood pressure <49 mmHg, serum pH <7.24 or Pa O2 <49 mmHg, or ventricular tachycardia to fibrillation;
- Haematology: WBC <1000/mm3, platelets <20000/mm^3, Ht <20%, Hb <7.5 g/dl;
- Renal: urine output <479 ml/24h or <159 ml/8 h, blood urea >100 mg/dl, serum creatinine >3.5 mg/dl;
- Respiratory: respiratory rate <5/min, PaCO2 >50 mmHg, or ventilator dependency > three days;
- CNS: Glasgow Coma Scale <5 (no sedation). Neurological dysfunction - agitation, disorientation, altered state of consciousness to schoolchildren.

At these conditions could be added at least one of the following (2): gastrointestinal signs: loss of appetite, vomiting, diarrhea, to acute gastrointestinal bleeding due to ulcer (caused by infectious stress), or dynamic ileus, intense meteorism. Clinical consequences of acute liver failure may include: jaundice, hepatosplenomegaly, total bilirubin level >4 mg%, ALT >2 x normal.

Insulin-dependent juvenile diabetes, can develop anytime, but generally occurs in children or young adults. The onset of the disease often follows a viral infection. As for the clinical case described below, it appeared in the context of sepsis.

Case report

We present the case of a young girl, 15 years of age (fig.1), who was admitted to the Pediatric Clinic Emergency Hospital Craiova on March 2010 (no. 11680).

The family does not report chronic diseases. She is the second child of young parents (35 and 39 years old); she was born at term, with birth weight 2600g. She was breastfed for the first six months and then nourished diversified, being weaned at three years only. After three years presented numerous (treated at home) respiratory tract infections; in school period was uncommon. The onset of acute illness was suddenly, with repeated vomiting, watery diarrhea, frequent abdominal cramps, asthenia, hypodinamism, and high fever (39-40°C), these symptoms appearing after eating a piece of chocolate. She was admitted to the Infectious Diseases Hospital where she has been treated with antibiotics and intravenous fluids for rebalancing. After two days she went into medium level coma, blood sugar level was 501mg/dl, urea 206 mg%, creatinine 4.3 mg%, ALT = 97 U/l and she was transferred to the Intensive Care Unit, where she kept undergoing insulin treatment and intravenous fluid rebalancing.

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Clinical characteristics were described as follows: height 156 cm, weight 49 kg, unconscious, suffering, ringed face, dry lips, oral-labial herpes, with necrotic lesion on her left flag, giant bullous lesion on her left calf (fig. 1), confluent petechial elements, disseminated both on the surface of the trunk and limbs, HR 99 b/min, BP 116/84 mm Hg, distended abdomen, moderate meteorism, loss of appetite, oliguria (<800ml/24 hours), she had no stool and no signs of meningeal irritation. Evolution in this patient presented eyelid swelling and legs' edema.

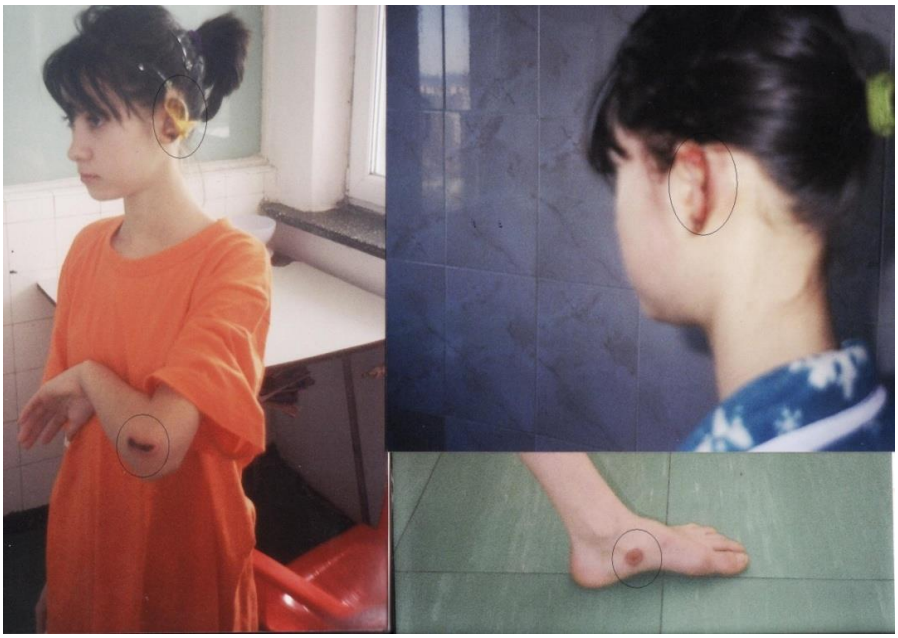

Fig.1: The teenager-patient suffering of diabetes and sepsis: skin necrotic lesions.

Laboratory investigations:

- Hemoleucogram was modified as follows:

Date	Hb(g%)	Ht (%)	Plt (mm^3)	WBC (mm^3)	Gs (%)	Lf (%)	Nn (%)
03 Mar 2010	11.6	32	191.000	14.300	15	15	5
04 Mar 2010	10.5	27	274.000	20.000	78	13	4
05 Mar 2010	9.2	27	299.000	15.800	82	10	4
08 Mar 2010	9.3	27	534.000	12.900	66	16	12
11 Mar 2010	8.8	27	413.000	11.600	65	18	9
16 Mar 2010	8.8	27	260.000	6.600	45	42	8

- ESR: 10 Mar 2010: 75/100 mm; 11 Mar 2010: 65/94 mm; 16 IMar2010: 40/60 mm.

- Urea and creatinine ranged as follows: urea rose steadily from 182 to 229 mg/dl and has been normalised (38mg/dl) after two weeks of treatment. Creatinine increased from 4.10 mg/dl at 6.53 mg/dl, then has reached the normal value of 0.81 mg/dl at discharged. Creatinine clearance: 44.12 ml/min.

- Exam Urinalysis: albumin fine trails, rare flat epithelium, leukocyte common, rare red blood cells. Urinary density 1005.

- Profile glucose: ranged between values 75-501mg/dl;

- Cholesterol 392mg%, triglycerides 265mg%, lipids 1078mg%;

- Astrup: Ph 7.31, pCO_2 29.3 mmHg, pO_2 25.9 mmHg, Bicarbonate 14.7; BE -10.2; Na 138 mEq/l, K 3,4 mEq/l, Cl 98 mEq/l.

- T Quick 40%, T Howell 140";

- Ex. pleural fluid cytology: relatively common mesothelial cells isolated and grouped, a few with hypertrophied nucleus, relatively rare, bare nuclei, relatively rare granulocytes leukocytes, red blood cells frequently.

- Chest X-ray: Consistent opacity with moderate, vague outline in the upper segment above basal right lower lobe, pulmonary type is opaque. At lung's base: opacities diffuse band with medium intensity.

- An abdominal ultrasound scan was performed: *no* intra-*abdominal pathology* was encountered.

- The patient's *hydroelectrolytic and acido-basic equilibrium* was restored, a dietetic therapy for the

management was provided along with a hyposodium and hypoproteic diete. Her medical treatment consisted of insulin therapy (1UI/kd/day), antibiotics, diuretics and Heparin. The dressings' lesions in her left calf have been daily changed.

After three weeks of intensive treatment, the evolution was slowly favourable: renal function recovering, blood sugar level stabilization and *epithelialization of skin lesions.*

At discharge, the patient has been recommended chronic treatment with insulin (4 doses), along with calculated carbohydrate diet and protein restriction on 35g/day for 1 year. A regular monitoring of renal function has also been recommended.

Discussions

Pathogenesis of type 1 diabetes is caused by autoimmune destruction of insulin-producing beta cells of the pancreas, usually after a viral infection. In this case, we have no data that would reveal a history-specific symptoms: polyuria, polydipsia, polyphagia with weight loss in the last month before admission. High sugar level was detected, two days after the abrupt onset of digestive disease. Serious gastrointestinal infection is likely to have precipitated the onset of diabetes or whether it is possible to produce it, due to severe sepsis. Severe sepsis is often associated with transient hyperglycemia (4), for many patients.

Diagnosis of sepsis was based on the presence of digestive infection as well as lung and skin one which pleads for SIRS criteria: onset of fever, leukocytosis over 12000 with a maximum of 20000 /mm^3 and tachypnea.

We suppose that the infection has been caused by gastrointestinal gram-negative bacteria whose endotoxins were spread to the bloodstream. These triggers stimulated inflammatory cytokines, interleukin such as: IL1, IL6, IL8, TNF, initiating the cascade of disseminated intravascular coagulation, both in macro and microcirculation. There has been also a direct toxic effect on the lung and kidney (5,6,7). Multiple organ dysfunction occured, as presented, at least for 24 hours: pneumonia, kidney failure, metabolic acidosis, vigil coma. Since the infection has been cured and endotoxins have been removed from bloodstream, renal function was recovered entirely.

She has also been discharged with insulin-dependent diabetes. After 2 years from MODS, girl teenager is equilibred. The single hospitalisation during this period was for a diabetic coma, one year ago.

Severe sepsis is quite frequent in intensive care units, being associated with a high rate both of morbidity and mortality. Usually, patients suffering from chronic diseases, such as: chronic hepatitis, HIV infection, cancer, are predisposed to sepsis and severe sepsis. Also, diabetic patients have high prevalence for infections as well as for sepsis (8,9).

Various authors have studied the pre-existing impact upon organ failures in sepsis and reached the conclusion that the diabetic patients develop kidney failure more frequently than the non-diabetic persons (10,11). However, there are still uncertain the causes that could influence these connections. It is very important though, to identify high-risk groups for acute organ failure that the mechanism involved might be understood and the treatment for these patients might be improved.

References

1. Angelescu N. Tratat de patologie chirurgicală, vol. 2, pag. 2120-2122.
2. Grigorescu-Sido P. – Tratat elementar de pediatrie – Editura Casa Cartii de Stiinta Cluj, 2000, vol. I pg. 91-92, vol. 4 pg. 441-450
3. Purcaru F, Georgescu I, Ciurea P, Cupşa A. – "Sepsis. Şoc septic. Disfuncţii multiorganice" (MODS) – Editura Medicală Universitară, Craiova, 2000, pg. 12-15; 11-13;231-274
4. Abraham E, Matthay MA, Dinarello CA. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. Crit Care Med. Jan 2000; 28(1): 232-5.
5. Burdette S.D, Parillo M.A. Systemic Inflammatory Response Syndrome, 2009, E Medicine.medscape. com/article168943.
6. Cupşa A – Boli infecţioase transmisibile. Ed. Medicală Universitară, 2007, pag:3.1-3.26;14.1-14.21.
7. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32(3):858-73.
8. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005 (1):2-8.
9. Harrison, Munford R.S. Principii de medicină internă, 2005, pg 852-857.
10. Esper MA, Moss M, Martin SG. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Critical Care 2009, 13:R18 (doi:10.1186/cc7717).
11. Kaplan SL. Bacteremia and septic shock. In: Textbook of Pediatric Infectious Diseases.2004:810-25.

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ASSESSMENT OF NEONATAL ANEMIA AND ITS IMPACT IN NEONATAL ADAPTATION

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Abstract

Anemia in the newborn can result from bleeding, hemolysis and deficiency in red blood cell production. Anemia at birth is mainly due to bleeding and immune hemolysis. Anemia blood loss can occur through obstetrical accidents, occult blood loss and internal bleeding. A retrospective study conducted in 236 anemic infants in the early neonatal period, hospitalized for neonatal anemia between January 1, 2010 and December 31, 2012 in "Bega" Clinic of Neonatology in Timisoara, identified an accumulation of significant risk factors influencing prognosis and treatment. Among infants with neonatal anemia, a total of 147 were premature. The most common cause of hemolytic anemia was the blood group incompatibility between mother and fetus, the prevalence being 9.55%.

Keywords: neonatal anemia, infants, gestational age, prematurity, pathology at birth

Introduction

In adults, the classic triad of hemolytic anemia is anemia, reticulocytosis and hyperbilirubinemia. Anemia in the early neonatal period can occur with minimal changes in hemoglobin values and even without increased reticulocyte values and has multiple etiologies, which can be grouped into three broad categories: isoimmunization, congenital and acquired defects of the erythrocyte [1]. The most common cause of hemolytic anemia is the blood group incompatibility between mother and fetus.

Anemia in the newborn period is divided into: hemolytic anemia, congenital abnormalities of erythrocyte membrane and hereditary erythrocyte enzyme abnormalities (deficiency of glucose-6-phosphate dehydrogenase and deficiency of piruvatkinasis) [1,2]. Hemoglobinopathies are congenital deficiency anemia hemoglobin and are divided into two groups: structural defects and defects in hemoglobin synthesis (thalassemia syndromes), which include: alpha thalassemia, hemoglobin H disease (deletion of three genes), fetal hydrops syndrome with hemoglobin. Bart, gamma thalassemia and beta thalassemia [2,3]. Hemolytic anemia due to won defects is divided into: anemia associated with infections, hemolytic anemia due to maternal autoimmune disease and neonatal anemia due to ineffective red cell production [1,2,3].

Hemoglobin values from umbilical cord increased steadily between 28 and 40 weeks of gestation. After expulsion, hemoglobin values and the number of erythrocytes decrease more quickly and early in premature infants. The speed and the size of the drop is proportional to the immaturity of the child [4,5]. In those with weight between 1.2 and 2.3 kg, hemoglobin values decrease to 9.6±1.4 g%, while in those with a birth weight less than 1.2 kg, the hemoglobin values decrease to 7.8±1.4 g%. Some children tolerate very low hemoglobin values without any sign of tissue anoxia, while others suffer obvious clinical problems, and the rapidity with the level of decreased can be significantly lower, that requires transfusion [6,7].

Anemia in early neonatal period is mainly due to bleeding and immune hemolysis. Hemorrhagic anemia can be caused by: obstetrical accidents, occult blood losses and internal bleeding. Occult losses before birth may be due to either fetal-maternal hemorrhage or transfusion between twins or placental hemorrhage [8,9]. The treatment management early after birth is crucial to a pale and shocked newborn: maintenance free upper airway and administer oxygen, umbilical artery catheterization for determination of hemoglobin, bilirubin, Astrup parameters, Coombs test, administration of plasma expander to maintain blood volume, finding the cause of bleeding. Jaundice control with phototherapy and transfusions are the most important aspects of therapy in the neonatal period [10,11,12]. Once the diagnosis is established, the infant will receive daily supplements of folic acid to meet the increased demands of the bone marrow in the process of erythropoiesis[13,14,15].

Materials and methods

The study material is represented by a homogeneous group of 236 infants with neonatal anemia during the years 2010-2012 Neonatology Clinic "Bega" in Timisoara. During this period there were 7703 births, of which 643 were premature babies. The cases studied were reviewing the various parameters that could be considered at risk for developing anemia in the newborn.

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Anemia neonatal of biologically was defined as a lack of hemoglobin (Hb <15g%). Particular attention was given to the number of erythrocytes (<4x106/mm3), hematocrit (<45%) and APGAR index, etc. Among infants with neonatal anemia, a total of 147 infants were premature. In all cases studied was prepared a special form in which the parameters were recorded anamnestic and clinical course. All parameters registered were essential to identify cases at risk of developing anemia in the early neonatal period. These parameters were analyzed in isolation and sequencing could make a contribution in the realization or worsening anemia.

The study is retrospective and seeks cumulative risk assessment and identification to the most at risk. Based on the assessments made by the study, we believe that identifying the percentage of cases with increased risk of developing anemia may be higher than those reported so far, and the purpose of this goal cannot be other than the establishment of early treatment and especially an effective prophylaxis, which could lead to anemia neonatal morbidity. The data collected in this study were processed using SPSS Statistics 17.

Results and discussions

In 2010-2012, in the Department of Neonatology "Bega" Timişoara were born a total of 236 children with a diagnosis of neonatal anemia. They were followed and studied under observation sheets of neonatology service in Timisoara. The prevalence of neonatal anemia in relation to the population of newborns in 2010-2012 is 3.06%. Share anemia is within 2.32% and 11.19% premature. We statistically analyze these cases the following parameters: Sex; The area of origin of the mother; Age of the mother; Weight at birth; gestational age; Hemoglobin values; Number of E; The values of mean corpuscular volume (MCV); Apgar score; The most common and less common 10 etiologies associated with neonatal anemia and the minimum values of Hemoglobin, in which the patient required blood transfusion.

Distribution of neonatal anemia by sex. Regarding gender distribution, one can observe a slight increase in the prevalence of female to male sex. The prevalence in males is 51.27% and female sex prevalence is 48.73%.

Distribution by origin area of mother. In urban areas, there is an increased prevalence of anemia compared to rural areas. Research shows that in rural areas, the prevalence is 46.19% compared to urban areas, where the prevalence is 53.81%. This increase is probably due to greater addressability of patients to the doctor attributed to the higher socioeconomic level, taking as evidence clearer and more extensive monitoring of pregnant women.

Mother's age. Regarding of maternal age at birth, studies show that most mothers who have children with anemia aged between 25 and 35 years, 63.98% of the study group. There is observed a marked increase in the incidence of neonatal anemia in newborns whose mothers are aged in risk groups:<18 years (2.97%) and>35 years (12.29%).Most mothers who have children born with anemia, are aged between 25 and 35 years, which shows that most children with anemia were born at a fertile age, but extremely busy both physically (age ascension at work) and mentally (tendency towards rumination on various topics, and put loads hormone-premenopausal).

Birth weight. Depending on the weight at birth, infants are divided into: preterm VLBW - with a birth weight below 1.000 grams, if they have a small share in the group of cases studied, only 1.69%.; preterm LBW with a birth weight between 1000-1500 grams, the study group represented 3.39%; preterm degree II, with a birth weight between 1500-2000 grams a procent of 5.93%.and preterm degree I, with a birth weight between 2000-2500 grams, with a procent of 11.02%. In total, prematurity by weight has a prevalence of 22.03%, which demonstrates that infants with a birth weight below 2.500 grams have a high risk of neonatal anemia. Newborn babies with normal birth weight over 2500 grams, which represent 77.97% of the study group. (Fig. 1)

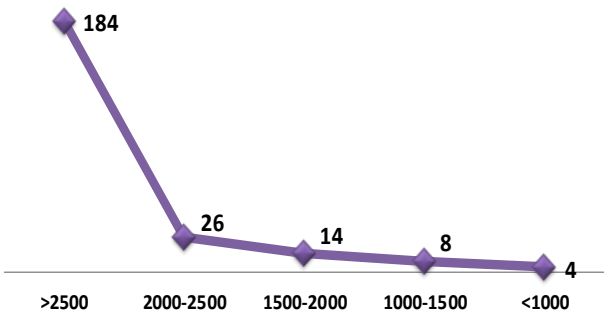

Fig. 1. The distribution of the weight of anemia neonatal birth.

Gestational age is the other criterion in infants anemic analysis. It is noted that prematurity plays an important role in the development of neonatal anemia, the prevalence is 62.28%. Most cases are found at a gestational age of 37-40 weeks (60.19%), followed by infants with gestational age of 33-36 weeks (22.03%). Extreme gestational ages, below 32 weeks, have a prevalence of 2.96%. Infants at term have a share of 37.71%, which leads to the conclusion that the risk of neonatal anemia is higher for preterm than for term infants. (Fig.2, Fig.3)

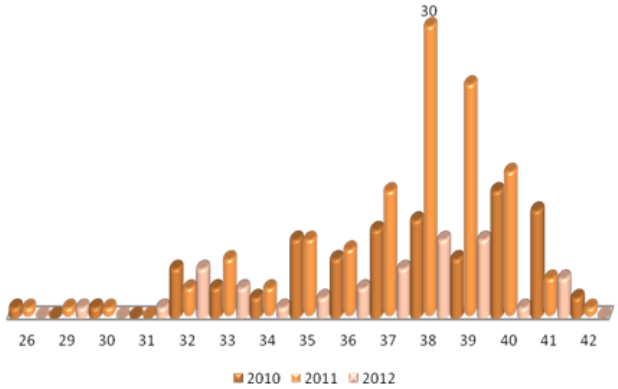

Fig. 2. Distribution of neonatal anemia after gestational age and years.

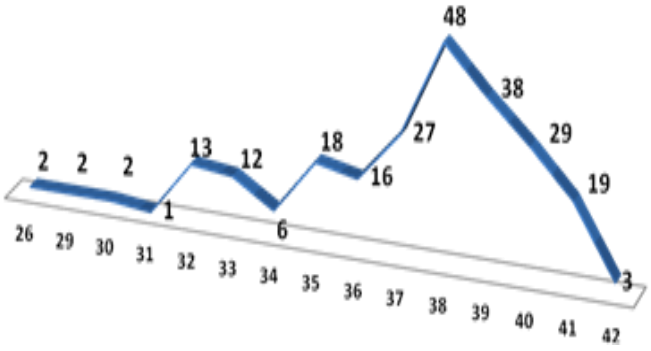

Fig.3. Distribution of neonatal anemia after gestational age.

Hemoglobin levels. In order to define neonatal anemia were considered hemoglobin levels below 15 g%. Thus there was a higher prevalence of hemoglobin values between 12 and 14.9 (70.06% in the preterm group and 73.30% in the reference group). (Table 1, Fig.4) This means that the degree of anemia present in these infants is mild.

Hematocrit values. Although relevant values to define anemia neonatal below 45% in the group also included patients with hematocrit values above this value (Table 2). Conventionally, we determined that hemoglobin is a major parameter in the diagnosis of neonatal anemia. Thus, as a parameter precipicant Ht is a factor of the degree of anemia. In this distribution we have seen that the rate of 89.11% of premature infants had Ht values between 30 and 45%.

Hb (mg%)	Year of Birth			Total
	2010	2011	2012	
<10	3	3	3	***9***
10-11,99	10	16	9	***35***
12-14.9	32	54	17	***103***

Table 1. Distribution of hemoglobin values in the study group by year of birth.

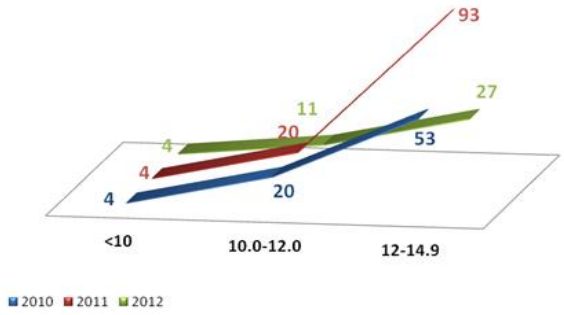

Fig. 4. Distribution of hemoglobin values in the study group by year of birth.

Table 2. Distribution of Ht values (%) in the study group.

Ht (%)	Year of birth			Total
	2010	**2011**	**2012**	
<30	4	7	4	15
30-45	67	106	37	210
>45	6	4	1	11

Distribution of red blood cells. The number of red blood cells is a highly sensitive parameter neonatal anemia. These are the ones that change the number in various pathologies anemia erythrocytes are cells that disrupted secondary pathogenic mechanisms.(Table 3, Table 4, Fig. 5)

Distribution of mean corpuscular volume (MCV). In the group of preterm infants, the proportion MCV below 90 fl, is 5.44%, and in the healthy infants this procent is 10.11%, which does not show a direct correlation between premature and NN VEM. (Fig 6)

Table 3. Distribution E (mil./mm3) in group of premature infants.

Nr. E (mil./mm^3)	Year of birth			Total
	2010	2011	2012	
<3	4	6	7	***17***
3-3.4	6	16	12	***34***
3.5-4	21	35	7	***63***
>4	14	16	3	***33***

Table 4. Distribution E (mil./mm3) in group of healthy infants.

Nr. E (mil./mm^3)	Birth year			Total
	2010	2011	2012	
<3	1	2	3	*6*
3-3.4	8	4	4	*16*
3.5-4	10	27	4	*41*
>4	13	11	2	*26*

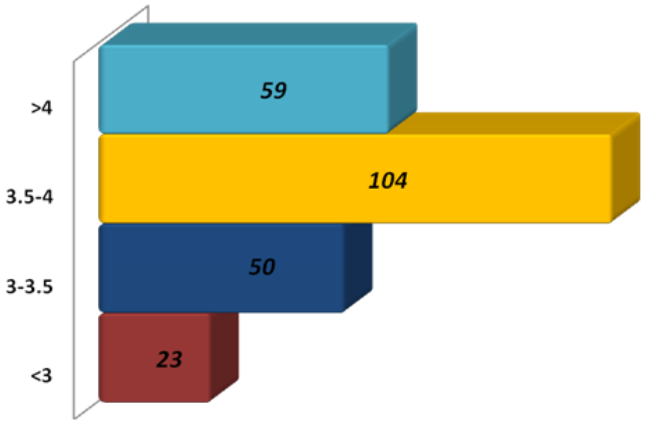

Fig.5. Distribution E (mil./mm3) in the study group.

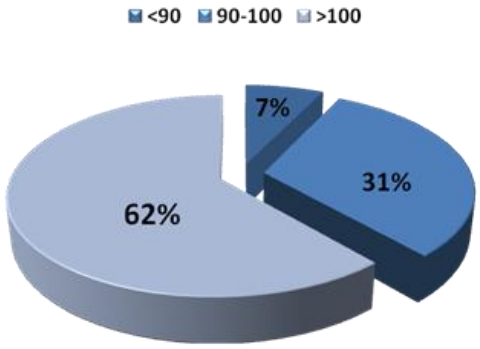

Fig. 6. Distribution of MCV (fl) in the study group.

The Apgar score is a very important criterion in the investigation of neonatal anemia. APGAR score between 8 and 9 has the highest prevalence of 65.25% in the study group. APGAR score 10 children with neonatal anemia developed, with an incidence of 15.25%. The Apgar score below 5 were presented only 1.27% of the children, showing that a score below 5 is not incriminated in the development of anemia. (Table 5)

A significant proportion have children with Apgar score between 5 and 7, representing 19.49% of the children. It seems APGAR score not affect the subsequent development of anemia.

The most common and less common 10 etiologies associated with neonatal anemia. In the study group has made use of more diagnoses, to develop a complete diagnosis, most infants with a complex pathology. (Table 6)

Table 5. Apgar score in prematurity group of infants.

APGAR score	Birth year			Total
	2010	2011	2012	
2	0	2	0	**2**
3	0	0	0	**0**
5	1	1	3	**5**
6	3	4	2	**9**
7	15	6	2	**23**
8	9	19	8	**36**
9	14	33	8	**55**
10	3	8	6	**17**

Table 10. The most common and least common etiologies associated with neonatal anemia.

	Etiologies	Total
1	Placenta praevia	1
2	Circular umbilical cord	6
3	Cephalhematoma right parietal	1
4	Twins	7
5	Acute intrapartum hypoxia	1
6	Acute intrapartum hypoxia+ ABO incompatibility	1
7	Circular umbilical cord+ acute intrapartum hypoxia+ventricular septal defect	1
8	Intrauterine growth restriction	1
9	Jaundice	7
10	Prematurity+sepsis	1
11	Prematurity+ acute intrapartum hypoxia	4
12	Circular umbilical cord+acute intrapartum hypoxia	5
13	Cesarian section	7
14	Prematurity	22
15	Other neonatal anemias	22

Minimum values of Hemoglobin, in which the patient required blood transfusion. A number of patients were diagnosed with severe anemia. with hemoglobin values below 10 g%.

Comparative analysis of the study group shows that neonatal anemia is better defined by reducing the total mass of circulating red blood cells than the decrease of hemoglobin value. For the diagnosis of neonatal anemia, in particular to preterm babies, it is necessary to collect all hematologic data, where the hematocrit is the most important. Clinical manifestations of neonatal anemia correlates significantly with some etiological perinatal circumstances and it is directly proportional to the damage degree of the total mass of circulating red blood cells. The assessment of preterm babie hematologic homeostasis damage, allows us to estimate the risk of developing late anemia[15].

Conclusions

1. Anemia in the newborn can result in bleeding, hemolysis and deficient in red blood cell production.

Anemia at birth is mainly due to bleeding and immune hemolysis.

2. Anemia blood loss can occur through accidents obstetrical, occult blood loss and internal bleeding.

3. A retrospective study conducted in 136 anemic infants in the early neonatal period, identified an accumulation of significant risk factors dictating the frequency and association prognosis and treatment.

4. The most common cause of hemolytic anemia is the blood group incompatibility between mother and fetus, as results from the study in the 136 newborns with anemia, where the incidence of anemia group incompatibility between mother and fetus is 9.55%.

5. Obstetrical accidents occur through normal umbilical cord rupture if precipitated unassisted births, but when the load as normal, but there are certain vascular abnormalities such as aneurysm of the umbilical cord, short cord circular cordon. It also can cause traction with forceps cord rupture.

6. Occult losses before birth may be due to either fetal-maternal hemorrhage or transfusion between twins or placental hemorrhage.

7. Injuries to internal organs during traumatic births are the most common causes of internal bleeding in the newborn. The most common areas of hemorrhage are subaponevrotic production, subperiosteal (cephalhematoma) and subarachnoid brain, liver, lungs, kidneys and spleen.

8. Neonates undergoing chronic blood loss in utero, at birth the different clinical conditions, from those with severe anemia requiring resuscitation immediately after birth to the asymptomatic mild anemia, requiring only iron supplement to increase hemoglobin and restoring iron stores.

9. The management immediately after birth is crucial to a newborn pale, shocked. Jaundice with phototherapy and control transfusions are the most important aspects of therapy in the neonatal period.

References

1. Aher S, Malwatkar K, Kadam S. Neonatal anemia. Semin Fetal Neonatal Med 2008; 13(4):239-247.
2. Ilie C., Neonatologie, ghid practic; Ed. Mirton, 2007, Timisoara; 100-125.
3. Lupea I. - „Tratat de Neonatologie” - Editura Medicală Universitara „Iuliu Haţieganu, Cluj-Napoca, 2005; 627-628;629-631.
4. Hinds LE, Brown CL, Clark SJ. Point of care estimation of haemoglobin in neonates. Arch. Dis. Child. Fetal Neonatal. 2007; 92:F378-F380
5. Quante M, Pulzer F, Blaeser A, Gebauer C, Kluge J, Robel-Tillig E. Effects of anemia on haemodynamic and clinical parameters in apparently stable preterm infants. Blood Transfusion 2013; 11(2):227-232
6. Strauss RG. Anemia of prematurity: pathophysiology and treatment. Blood Rev 2010; 24(6):221-225.
7. Urbaniak SJ, Greiss MA. RhD hemolytic disease of the fetus and the newborn.Blood Rev. 2000; 14:44-61
8. Jang DG, Jo YS, Lee SJ, Lee GS ,Risk factors of neonatal anemia in placenta previa; Int J Med Sci. 2011;8(7):554-7. Epub 2011 Sep 19.
9. Radlowski EC, Johnson RW. Perinatal iron deficiency and neurocognitive development; Front Hum Neurosci. 2013 Sep 23;7:585
10. Iorgulescu M. Terapia cu sânge şi derivate de sânge în stările morbide ale nou-născutului. A 3-a Conferinţă Naţională de Medicină Perinatală cu participare internaţională, Timişoara, 7-9 octombrie, 1999; 19-30 (Vol. Conf).
11. Bishara N, Ohls RK. Current controversies in the management of the anemia of prematurity. Semin Perinatol 2009; 33(1):29-34.
12. Ted Eastlund, M.D, Transfusion Therapy: Clinical Principles and Practice; N Engl J Med 2005; 352:2562-2563June 2013.
13. Hosono S, Mugishima H, Shimada M, Minato M, Okada T, Takahashi S, Harada K. Prediction of transfusions in extremely low-birthweight infants in the erythropoietin era. Pediatrics Int 2006; 48(6):572- 576.
14. Haiden N, Schwindt J, Cardona F, Berger A, Wald M, Kohlhauser- Vollmuth C, Jilma B, Pollak A. Effects of a combined therapy of erythropoietin, iron, folate and Vitamin B12 on the transfusion. Requirements of extremely low birth weight infants. Pediatrics 2006; 118: 2004-2013.
15. Richard H. Sills,Albany N. Y., Practical Algorithms in Pediatric Hematology and Oncology; Karger Ed., Basel,2003, 4-27.

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DOWN SYNDROME ASSOCIATED WITH THE NEONATE INFECTION PATHOLOGY

Marioara Boia[1], Aniko Manea[1], Daniela Cioboata[2], Diana Rogobete[2]

Abstract

The Down syndrome is a chromosomopathy characterized by the presence of a supplementary 21st chromosome, with particular phenotypic appearance.

The authors have an analysis of immediate and from distance prognostic of the patients from the study to which the pathology especially the brunk infection reduces the distance prognostic.

The study was done at the Neonatology and Children Clinics over a period of 4 years. In the study was included 36 patients which presented clinical picture characteristic to the syndrome associated with specific changes of the karyotype.

Newborns with Down syndrome have presented infection pathology associated with malformation syndromes (cardiac) which extend the length of hospitalization on the one hand and clinical-biological recovery on the other hand.

Keywords: Down syndrome, infection, new borns

Introduction

The Down syndrome represents an interdisciplinary complex pathology during childhood period, especially for newborns, with an incidence of 1 out of 700 births(1).

It's a chromosomopathy characterized by the presence of a supplementary 21st chromosome, which, clinically, leads to a complex picture, with particular phenotypic appearance, delay in acquisitions(5, 7) associated or not with isolated or combined cardiac, digestive or osteo - articular malformations,.

For all the women with risk (above 35 year old, existence of trisomy inside the family), the amniocentesis allows prenatal diagnosis (5) and interdisciplinary genetic counseling, but the attitude towards the pregnancy is fully of parents in concordance with moral, religious and ethnic principles of the family.

Objectives

In this paper, the authors have an analysis of the pathology associated with Down syndrome, which leads to an increase of the hospitalization period and complications. In the same time it is realized an analysis of immediate and from distance prognostic of the patients from the study group to which the pathology especially the bunk infection reduces the distance prognostic.

Materials and methods

The study was done at the Neonatology and Children Clinics over a period of 4 years. From a total of 3270 patients, 36 were included in the study which presented clinical picture characteristic to the syndrome associated with specific changes of the karyotype (fig. 1).

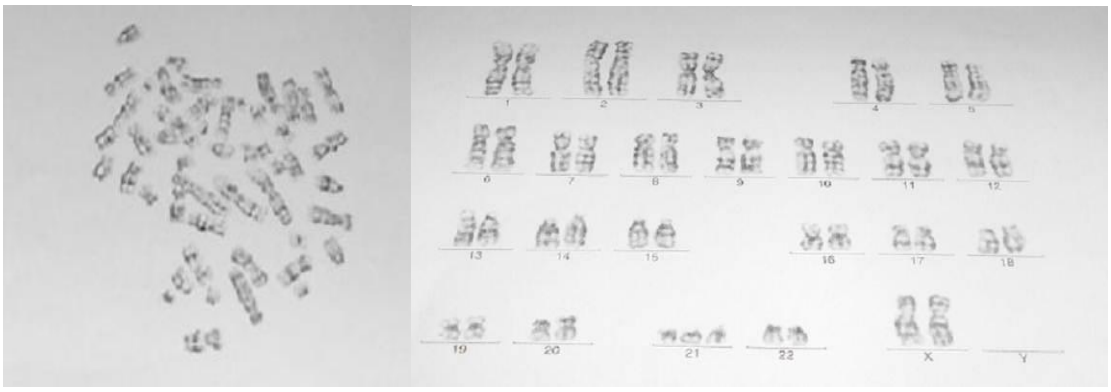

Fig. 1. Karyotype 47, xx+21.

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Cytogenetic diagnostic of 21 trisomy was presents in 34 children (94.44%) and only 2 cases (5.56%) had the mosaic. The investigations were done precocious postnatal after the specific clinical signs were indentified.

The work method was represented by retrospective analysis of patients' observations papers and also by dynamic analysis of clinical and biological picture of hospitalized patients (6 cases) from the beginning of the study.

In the study were included patients with: typical malformation phenotype, specific changes of the karyotype, clinical and biological picture which complements the positive diagnosis.

Complex laboratory investigations and multiple interdisciplinary consults were done: genetic, cardiologic, endocrinology, pediatric surgery.

Results and discussions

The presence of homogenous trisomy 21 was high to the group of study (94.44%) similar with the data from literature (90-95%) (6), unlike the mosaic (5.56%) (fig. 2) higher than literature (1-2.5%) (7). Inside the group of study we didn't have cases of translocation.

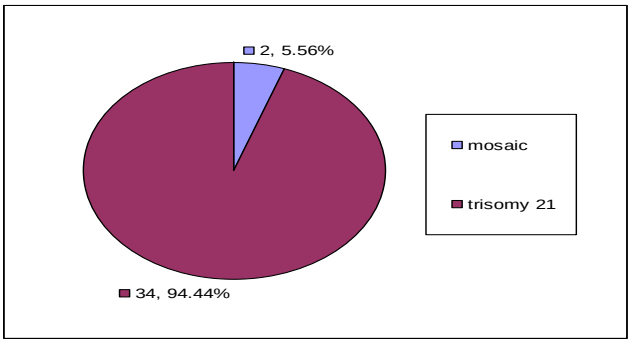

Fig. 2. Cases repartition after karyotype aspect.

The analyses of personal history, for placement in categories of newborns highlights a high proportion of premature children, 22 cases with gestational age less than 37 weeks and 14 term infants. Regarding the birth weight in 77.77% of cases the intrauterine growth retardation was present.

The phenotypic appearance is characterized by: brachycephalic head, with flattened occiput and broad fountains (7); round face "moon face", flat (7); epic (1); oblique fissure vents up and out (1); small nose with flattened root , small nostrils and anteversion (5) was present all the cases from the study.

Some clinical signs like open mouth, with tongue protrusion – pseudomacroglosie (6); small, dysplastic and lower inserted ears (7); short neck, with excess skin on the scruff (6); short, broaded and with brachydactyly hands (shortened fingers), clinodactyly (no bowing fifth finger) and a single palmar flexion crease (simian crease) (7) were present in varying proportions, except the simian fold, frequent sign to the patients with Down malformation, present in 78% of cases, which coincides with literature numbers.

Mental retardation present in all patients ranged from severe to moderate.

The pathology malformation was present, single or in combination, the proportion of patients without any malformation was little (6.7%), higher than the literature data (5.9%) (2), remark for predominance of cardiac malformations (ventricular septal defect - 44.44% vs.12-35% (2), atrial septal defect - 19.44% vs.5-38% (2), atrio-ventricular canal - 16.66% vs.3-55% (2)), musculoscheletal malformations (congenital clubfoot – 30.55% , polydactyly - 8.66%, syndactyly- 5.55%) (fig. 3).

The gastrointestinal anomalies were present in the proportion of 13.86% vs. 4-11% (2) to five patients (two patients with duodenal stenosis surgery, a patient transferred in Pediatric Surgery Service, a case of duodenal atresia type one surgery, a case of paralytic ileus).

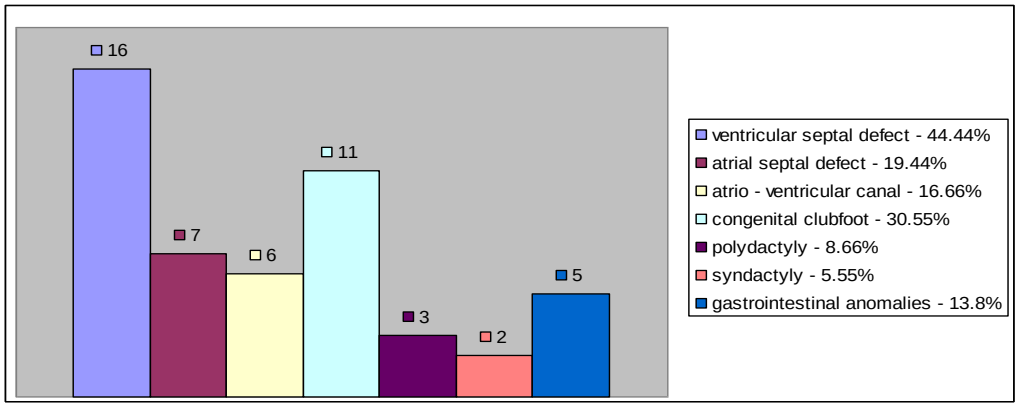

Fig. 3. Cases repartition depending on associated malformation.

All patients under study had deficient diet, absent sucking reflex – 72.22% cases, sucking - swallowing incoordination, that determinates a constant weight deficit, with growth disorders, weight curves slowly ascending, which leads to increased length of hospitalization.

Average length of stay to children with Down malformation was 45-60 days, in contrast to literature data which states much lower average length about a week (5) to the newborns at term with Down Syndrome.

The increased of average length of stay in association with immunological deficits specific to neonatal and child at breast period on the one hand, and the other hand associated to the affection, have increased the incidence of infections and the growing of their severity.

The specific immunodeficiency to Down syndrome includes following association: mild to moderate lymphopenia of T and B cells, with marked decrease of naïve lymphocytes, the affect of proliferation of T cell mitogen-induced, the reduction of specific antibody responses to vaccinations and defects of neutropfil chemotaxis. Secondary immunodeficiency due to nutritional or metabolic factors in Down syndrome and the deficiency in zinc were cited. Non-immunological factors, including abnormal anatomic structures (for example the small ear canal, tracheomalacia) and the gastro-esophageal reflux play a role in increasing the frequency of respiratory tract infections, found in our study for 2 cases. The molecular mechanism leads to immune defects observed to individuals with Down syndrome and the contribution of these immunological anomalies to the increased risk of infections requires further investigation. The approach of immunological and non-immunological factors involved in the pathology of the infectious diseases can reduce the infections susceptibility to individuals with Down syndrome (4).

From the group of study 3 cases had an unfavorable evolution to death due to pathology of associated malformation: cord malformation, neonatal sepsis and necrotic enterocolitis ulcerative.

So, to the group of study the neonatal septicemia was present at 36.11% cases, whereas localized lighter forms were: congenital pneumonia – 16.66%, necrotic - ulcerative enterocolitis -11.11%, other infections 36.1% (fig. 4).

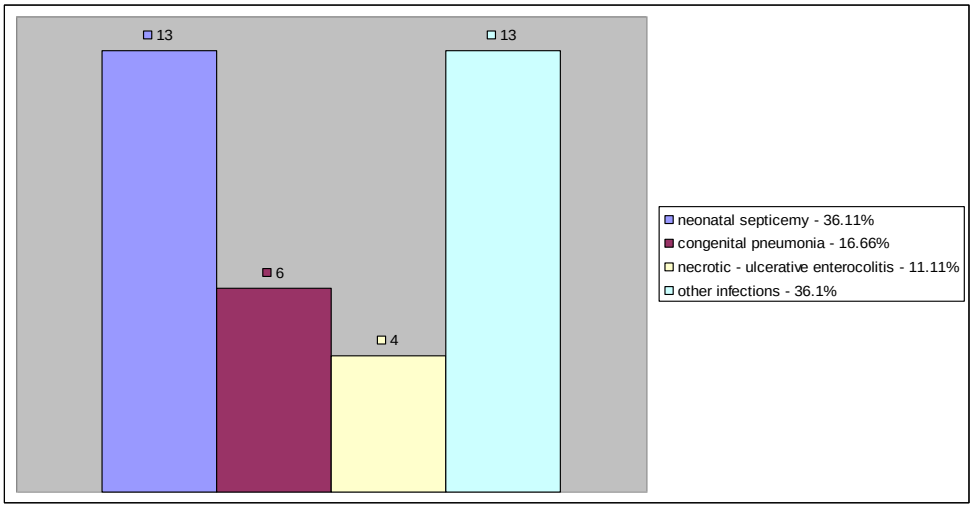

Fig. 4. Infection cases repartition.

The septicemia cases have presented train evolution which resulted in clinical and biological late recovery with increasing duration and cost of hospitalization.

Diagnosis was easily established based on positive cultures, positive blood cultures, evidence of positive rapid inflammatory (persistent and severe thrombocytopenia, highly positive C-reactive protein, positive procalcitonin with values over 7-8-12 ng/ml, severe leukocytosis).

From bacteriological point of view in neonatal septicemia with early onset the results attest presence of gram-negative bacilli in proportion of 94% with predominance of Pseudomonas Aeruginosa (44%), followed by Serratia Marcenses and Klebsiella Pneumoniae and in 6% of cases the coagulase-negative staphylococcus is present (fig. 5). According to the specific literature, in 30-40% cases the principal factor involved in neonatal septicemia with early onset is the group B streptococcal (4).

In septicemia with late onset germs most frequently involved are also gram-negative bacilli (77%), but the most common is Serratia Marcenses, followed by Klebsiella Pneumoniae and Pseudomonas Aeruginosa (fig. 6). 23% from microbial flora is formed by gram-positive cocci. (3)

Regarding the onset: 5 cases have presented early onset in the first 5 days of life, what sustains intrauterine infection of the newborn, 8 cases have presented late onset due to prolonged hospitalization, specific immunodeficiency and associated malformation syndromes.

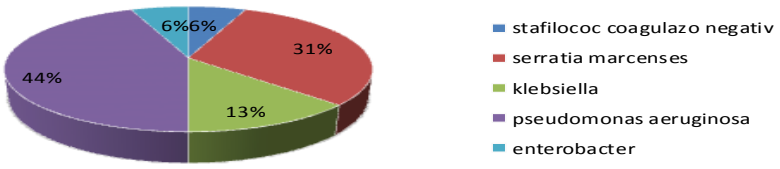

Fig. 5. Incidence of microbial flora in early onset septicemia.

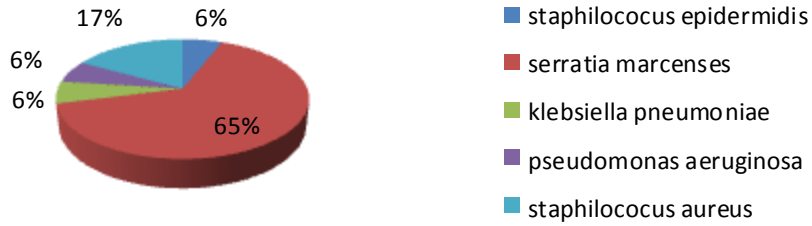

Fig. 6. Incidence of microbial flora in late-onset septicemia.

Conclusions

1. Newborns with Down syndrome have presented infection pathology associated with malformation syndromes (cardiac) which extend the length of hospitalization on the one hand and clinical - biological recovery on the other hand.

2. Cytogenetic diagnosis made earlier and to all patients from study highlights a predominance of trisomy 21 (94.44%) and the mosaic (5.56%). We don't have translocation cases to patients from the study.

3. For group of study we didn't observed a correlation between the intensity of phenotypic characters, the prevalence and the intensity of clinical and biological manifestations. But it was observed a correlation with the associated malformations, their intensity, evolution and prognostic beeing much hampered to patients with associated malformations.

References

1. Mihai Gafencu, Maria Julieta Puiu, Violeta Stan, Gabriela Doros - Sindromul Down de la ingrijire la intelegere si acceptare (Brumar 2005)
2. Raluca Maria Vlad, Paula Grigorescu Sido, Simona Bucerzan, Camelia Al-Khzouz, Ioana Nascu, Eugen Pascal Ciofu - Sindromul malformativ la pacientii cu trisomie 21(Revista Romana de Pediatrie vol. LXI, nr. 4, year 2012)
3. Marioara Boia, Constantin Ilie, Aniko Manea, Daniela Iacob, Daniela Cioboata, Florentina Handrea -Neonatal Septicemia- Retrospective Study On Premature Newborn (Jurnalul pediatrului, year XIII, vol. XIII, nr. 49-50, january-june 2010)
4. GAO-11-57 - Children with Down Syndrome (October, 2010)
5. Laurie Barclay - Risk for heart, lung disorders increased in VLBW infants with Down, s Syndrome, (November, 2010)
6. Susan N Van Cleve, William I Cohen - Clinical Practice guidelines with Down Syndrome from birth to 12 years (J Pediatrics health Care 2006);
7. Judith Rankin, Peter W. C. Termant, Many Bythell - Predictors of survival in Children Born with Down Syndrome : A Registry Based Study (2012)
8. Barbara J Stoll, Jeffrey C Murray, Michelle C Walh - Survival and morbidity outcomes for Very Low Birth Weight infants with with Down Syndrome (J Pediatrics Health Care 2010)
9. G. Ram, Chinen J. – Infections and Immunodeficiency in Down syndrome; (Clinical and experimental Immunology vol. 164, year 2011)
10. G. Brad, Ioan Sabau, Ioana Micle, M. Boia – Sepsis in newborns (Timisoara Medical Journal 2010)

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A RARE CASE OF INCONTINENTIA PIGMENTI WITH SEVERE EXTRACUTANEOUS MANIFESTATIONS

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Abstract

Incontinentia pigmenti (IP) is a complex genodermatosis inherited in an X-linked dominant pattern, associating multistadial cutaneous manifestations with an oculo-dento-cerebral syndrome, which affects only female newborns, as the disorder is lethal in males since intrauterine period. We report on a case of incontinentia pigmenti with an atypical debut consisting of tonic-clonic seizures which had started during the first days of life, associated with severe ocular and neurologic manifestations. The presence and severity of extra-cutaneous features most often command the evolution and the prognosis of the disease.

Keywords: incontinentia pigmenti, genodermatosis, apoptosis

Introduction

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a genetic disorder inherited in an X-linked dominant pattern, characterized by cutaneous, neurologic, ophthalmologic and dental abnormalities, only present in female new-borns because males do not survive until birth (1). It is a rare disease with a prevalence of 1/50.000 in general population (2). Its pathogenesis seems to be related to the induction of cellular susceptibility to tumor necrosis factor-induced apoptosis in the cells presenting mutations of a gene situated in the Xq28 region of the X chromosome (1)

Clinical case

We report on a case of a female new-born with a birth weight of 3200 g, APGAR 9 score, resulted from a normal pregnancy, hospitalized, without any perinatal pathological history, which since the first 2 days of life presented tonic-clonic generalized seizures that remised after intravenous administration of diazepam. The first seizures were succeeded by the appearance of a cutaneous rash, first presenting as patches and then, after 5 days of life, consisting of vesicles and bullae disseminated on the limbs and trunk. From the physiological history of the mother, we note primiparity and the existence of an induced abortion.

When addressed our clinic, at the age of 14 days, the patient presented light brown pigmented patches with reticular pattern, vesicles and bullae, as well as verrucous lesions located on the limbs and trunk, arising on place of previous vesicles and bullae. Laboratory findings showed leukocytosis associated with neutrophilia and elevated C-reactive protein (CRP) level; lumbar puncture revealed pleocytosis associated with neutrophilia in the cerebrospinal fluid (CSF) and the transfontanelar ultrasound examination revealed two right choroid plexus cysts and second degree right retinal hemorrhage. Cutaneous cultures proved *Klebsiella spp*. and the skin biopsy revealed suggestive histopathologic aspects asserting the clinical diagnosis of incontinentia pigmenti- verrucous stage.

Under antibiotic treatment (Vancomycin 15 mg/kg/dose administered every 8 hours and Gentamycin 4 mg/kg/dose administered every 24 hours), anticonvulsant (Diazepam 0.3 mg/kg/dose, followed by sodium valproate-Depakine p.o increasing the dose gradually until achieving the maintenance dose of 30 mg/kg/day divided into 3 doses administered every 8 hours) and symptomatic treatment, the evolution was unfavorable, with seizure persistence, subsequent development of generalized porencephalic lesions located in both cerebral hemispheres and progressive deterioration of the medical status that led to exitus at the age of 5 weeks.

Discussion

IP is a genodermatosis inherited in an X-linked dominant pattern that most frequently affects female new-borns; it is usually lethal in males since the very intrauterine period (3). In 63% of the cases incontinentia pigmenti is ascertainable since birth or appears during the first week of life, rarely during the first year and even less frequently after the first year. IP is a complex genodermatosis that associates cutaneous changes with an oculo-dento-cerebral syndrome (4).

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Even though a similar case was described in the literature in 1906 by Garrod, the historical credits for the first description of the condition are attributed to Bloch (1926) and Sulzberger (1928). In the past, the disorder has also been called Ashoe-Hansen disease, Bloch-Siemens syndrome, Bloch-Siemens pigmented dermatosis or melanoblastosis cutis linearis (3). Bloch named the disease after he observed that the melanic pigment, instead of passing from the basal layer of the epidermis into the squamous cell layer, is not retained in the epidermis and passes into the dermis, where it is captured by macrophages, producing an effect similar to tattooing, without a real excess in the production of melanin (5)(6)(7).

The pathogenesis of IP is associated with mutations in the gene coding the nuclear factor kB essential modulator (NEMO, NF-kB essential modulator), a 23 kb gene situated on the Xq28 chromosome (2). An important deletion of the 4-10 exons of NEMO (the NEMOΔ4–10 mutation) can be detected through Southern Blot analysis or PCR diagnosis in 85% of the patients with IP, while other mutations such as nucleotide substitutions, various deletions or insertions occur in only a small number of patients (6)(8).

The NEMO gene encodes a protein called IKKγ, which along with the IKKα and IKKβ proteins form IKK (IkB kinase). IKKα and IKKβ have a catalytic role, while IKKγ has a regulatory role (9)(10).

Normally, NF-kB is inactive and does not activat transcriptions of genes in the nucleus, being confined in the cytoplasm after binding to its specific inhibitory, IkB (kB inhibitory). IKK will phosphorylate IkB at the level of two serine residues, which leads to the unfolding of the connection between IkB (which will subsequently be degraded by proteosomes) and NF-kB and allows the latter to migrate unabashed towards the nucleus, where it will bind to the DNA at the level of numerous target genes that present sites for NF-kB attachment and whose transcription will be activated. NF-kB target genes regulate the cellular growth and proliferation and the production of membrane receptors, cytokines and various adhesion molecules. Besides those, an important target of NF-kB at the nuclear level is represented by the IAP genes (inhibitors of apoptosis proteins), genes that encode a set of proteins that block the caspase activity, stopping the apoptosis. Therefore, NF-kB is also involved in cellular survival response, inhibiting the apoptosis triggered on extrinsic pathway by TNF α.

The apoptosis triggered by TNF on extrinsic pathway starts with the binding of tumoral necrosis factor (TNF) to its receptor TNFR-1, event which induces a conformational change of the intracellular domain of TNFR-1, leading to the release of SODD (silencer of death domains), a 60 kDa protein that inhibits the reciprocal interaction between the tanatogenic intracelular domeins of TNFR-1, therefore blocking the accidental activation of the apoptotic pathway. In the absence of SODD, TNFR-1 receptor becomes able to recruit TRADD (TNFR associated death domain), an adaptor protein which itself will recruit and bind other proteins, such as RIP (receptor interacting protein) or TRAF-2 (TNFR associated factor). The latter will activate NIK (NF-kB inducing kinase), which will activate the IKK complex, which will phosphorylate IkB, which in turn will release NF-kB nuclear factor (9). Thus, the alteration of NEMO gene modulates the susceptibility of the cells to apoptosis, which might explain, at least partially, the intrauterine death of males (fig.1) *(2)(6)(10).

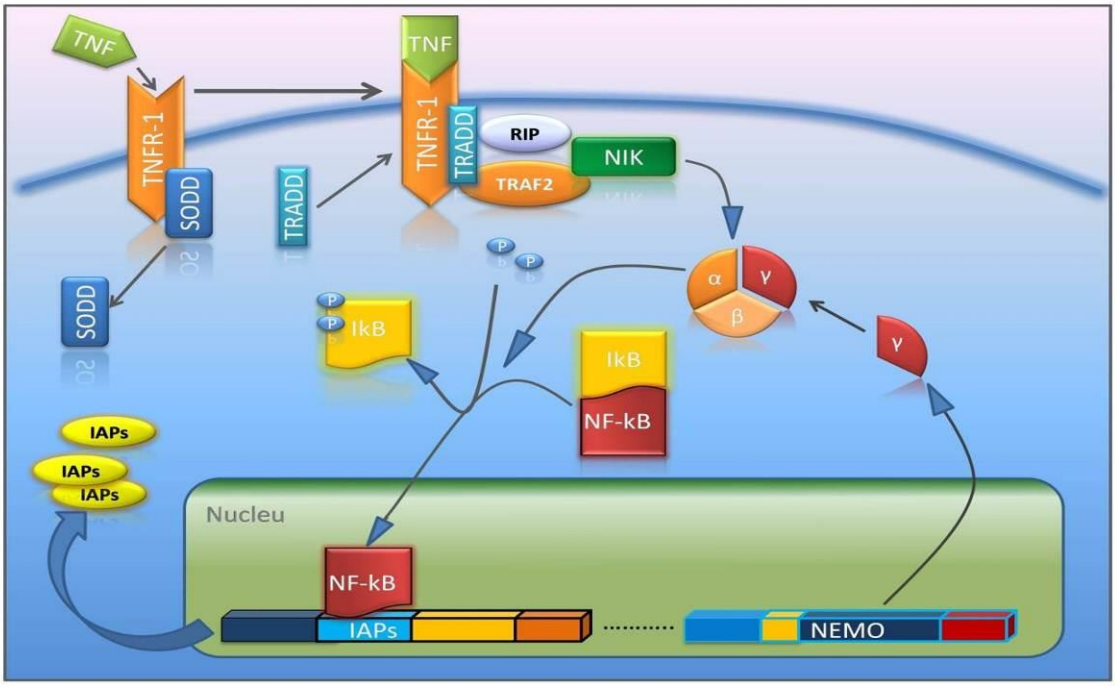

Fig. 1- Nuclear factor kB regulation and mechanism of action; TNF-Tumor Necrosis Factor, TRNFR-1 – TNF-Receptor 1, SODD –Silencer of Death Domains, TRADD-TNFR-associated Death Domain, RIP-Receptor Interacting Protein, TRAF-2- TNFR Associated Factor 2, NF-kB – Nuclear Factor kB, P-phosphate groups, NIK- NF-kB Inducing Kinase, IkB –Inhibitory of kB, NEMO-gena NF-kB essential modulator, IAPs-Inhibitors of Apoptosis Proteins.

Moreover, it has been demonstrated that the NEMO deletion only determines inflammation in the keratinocytes exposed to TNF and that the induced absence of TNFR-1 (TNF receptor 1) cancels the appearance of inflammation, aspect which contributes to the hypothesis according to which the cells which present mutations of the NEMO gene are destroyed by TNF induced apoptosis. Te subsequent destruction of the cells may explain, at least partially, the healing of the lesions and the multistadial aspect found in the evolution of the disease (9). Another role in the pathogenesis of the disorder is attributed to eotaxin, a chemokine whose cutaneous expression is stimulated by TNF; eotaxin has an eosinophil chemotaxis role, their accumulation and the degranulation in the epidermis explaining, among others, the formation of vesicle-bullae following the action of their proteolytic enzymes on the desmosomes and tonofilaments (3)(11)(12).

IP is classically considered a lethal disease in males, with few exceptions. Male patients with clinical features resembling the ones that appear in females with IP- more accurately the four characteristic dermatologic stages and ocular anomalies- are extremely rare and generally have a 47XXY kariotype (Klinefelter syndrome) (10)(13). Also, the postzygotic mutation and somatic mosaicism have been recognized as mechanisms which can explain the survival of males with IP (13)(14)(15). In the case we are presenting, the patients' mother was primipar and had presented, two years before, a provoked abortion, with no history of previously lost pregnancies.

Cutaneous manifestations in IP are frequently the first observed and are classified in 4 stages:

Stage 1- vesicular or inflammatory stage: occurs in 90% of the patients, usually at birth or during the first week of life; there have also been described cases in which the lesions had appeared after the age of one year. This stage is characterized by the development of erythematous patches and vesicles/bullae with a linear pattern and inflammatory base, which can transform to pustules by superinfection. In most cases the trunk and the extremities are affected. Vesicles usually disappear spontaneously after a few months (3)(16)(17).

Stage 2- verrucous stage: is seen in 70% of patients, usually appearing between the weeks 2 and 6 of life. As the vesicles dry, verrucous, hyperkeratotic, papules and plaques with a linear pattern, and rarely, lichenoid papules develop in their place. In 92% of cases the lower limbs are affected. The lesions disappear in 80% of the patients by the age of 6 months (3)(17).

Stage 3: is seen in 98% of the patients and is characterized by the development of streaks of brown or gray pigmentation along the Blashko lines, often resembling "chinese letters"; they most often involve the trunk and limbs and do not derive from the lesions that characterize the previous stages. The nipples, axillas and genitals are frequently hyperpigmented; the hyperpigmented areas do not usually correlate to the areas affected in the previous stages. The onset of the stage is generally at the age of 16-26 weeks and the lesions persist for years or decades, until puberty or adulthood (3)(16).

Stage 4- the cutaneous features arise after the resolution of vesicle-bullae and verrucous lesions, often before the disappearance of hyperpigmentation and consist of hypopigmented and atrophic areas, lacking sudoripary secretion. Generally the lesions are located on the limbs; these lesions are permanent and can often be the only sign of cutaneous involvement in adults (3)(16).

Our patient presented a typical progression of the cutaneous features, with the appearance of vesicle-bullae on the limbs and trunk during the first days of life and their healing with the occurrence of verrucous lesions at the age of 14 days (fig.2).

Extracutaneous abnormalities are associated in approximately 80% of the cases (table 1) (3)(4)(16)(18)(20).

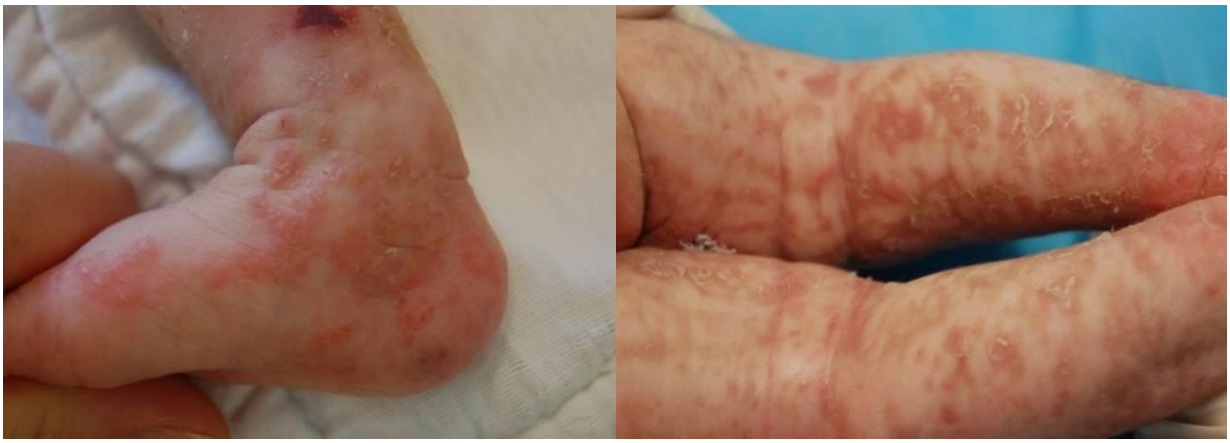

Fig. 2 – Clinical appearance at the age of 14 days: vesicles and bullae, as well as verrucous lesions located on the upper limbs and the distal third of the lower leg; light brown pigmented patches with reticular pattern located on the trunk and the lower limbs.

Table 1. Extracutaneous abnormalities:

- central nervous system (30% of cases) abnormalities: microcephaly, hydrocephaly, seizures, epilepsy, motor disturbance, mental deficiency, aseptic encephalomyelitis, EEG abnormalities;
- dental abnormalities (80% of patients) include partial anodontia, delayed eruption of dentition, conial or pegged teeth, anomalous crowns, etc.
- bone anomalies (20% of patients): skull deformities, kyphoscoliosis, hip dislocation, etc
- congenital cardiopathy : rare
- other anomalies: nanism, cleft lip and palate, ear anomalies, spina bifida.
- ophtalmologic findings: are frequent, usually asymmetric, and include: nystagmus, strabismus, microphthalmia, conjunctival pigmentation, corneal scars, irregular iris pigmentation, congenital cataracts, retinal detachment, optic nerve atrophy, vitreous anomalies or hemorrhages, persistent hyaloid artery, myopia.
- nail features: nail dystrophy and pitting that appear in 7-40% of the patients during childhood and usually disappear as the years go by (3).

In our patients' case, she presented neurological anomalies since birth, respectively generalized tonic-clonic convulsions and ophthalmologic abnormalities consisting of retinal hemorrhage which accompanied the cutaneous features, represented by a patch eruption that transformed during the first days of life into a vesicular and then verrucous eruption.

The diagnosis is initially based on clinical criteria (18). The skin biopsy is useful, showing changes that vary depending on the stage of the cutaneous features. In this particular case, the histopathologic examination proved moderate hyperorthokeratosis and focal parakeratosis including polymorphonuclear cells (eosinophils) forming abscesses loated in stratum corneum, moderate acanthosis and papillomatosis and frequent transepidermal dyskeratotic keratinocytes; moderate spongiosis with focal eosinophil exocytosis, dermal edema, capillary ectasia, minimum inflammatory infiltrate with frequent eosinophils and minimal vacuolar degeneration of the basal layer of epidermis were also observed and are consistent with the diagnosis of incontinentia pigmenti-verrucous stage (fig.3).

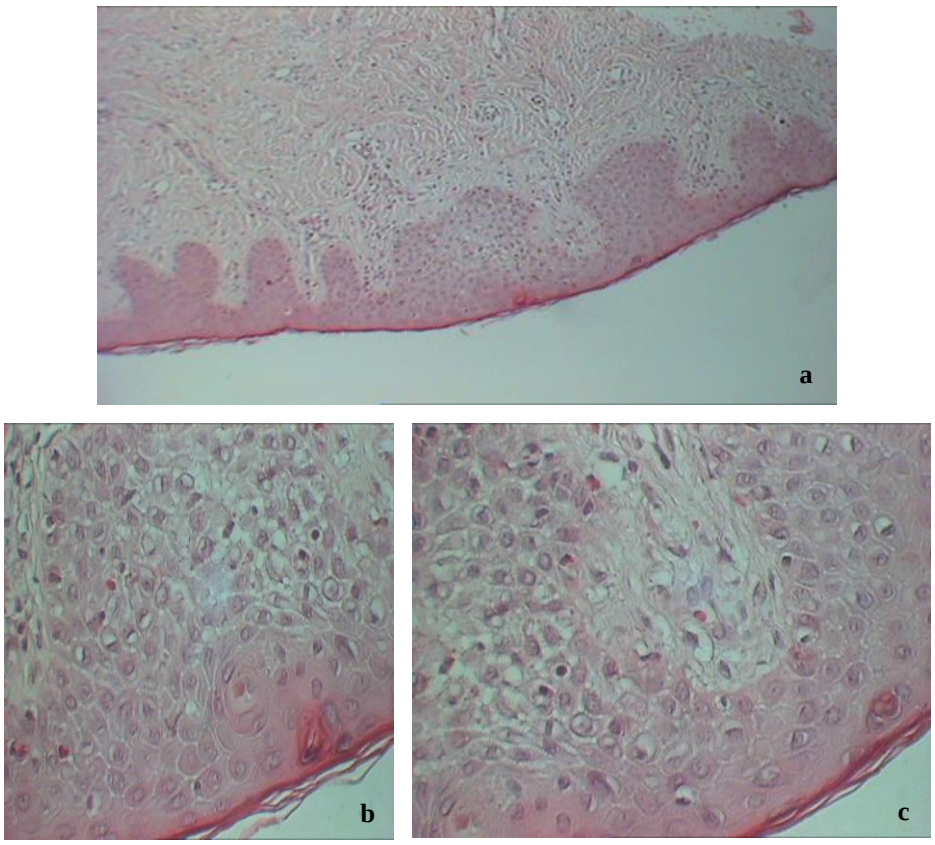

Fig. 3 – Histopathological examination of skin lesions, H-E, magnification 10X(a), 20X (b) and 40X (c) – detailed explanations in the text.

Neuroimagistics is recommended when neurological or ophthalmological anomalies are suspected. In our patients' case, the eye fundus examination proved the presence of retinal hemorrhage (fig. 4) and the transfontanelar ecography revealed disseminated porencephalic lesions, bilateral hydrocephaly and the presence of two right choroid plexus cysts (fig.5).

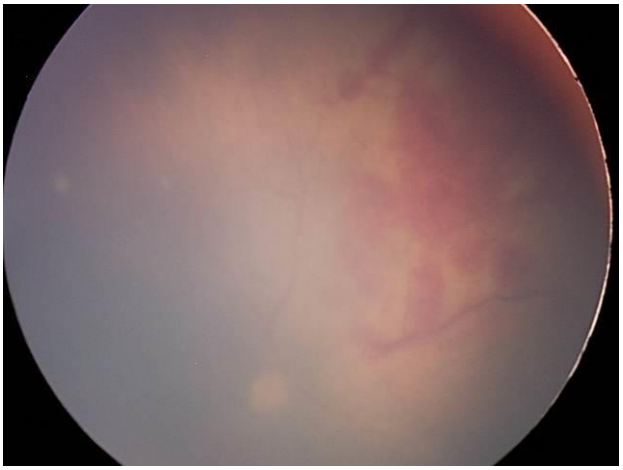

Fig. 4 – Eye fundus examination of right eye proving the presence of second degree retinal hemorrhage.

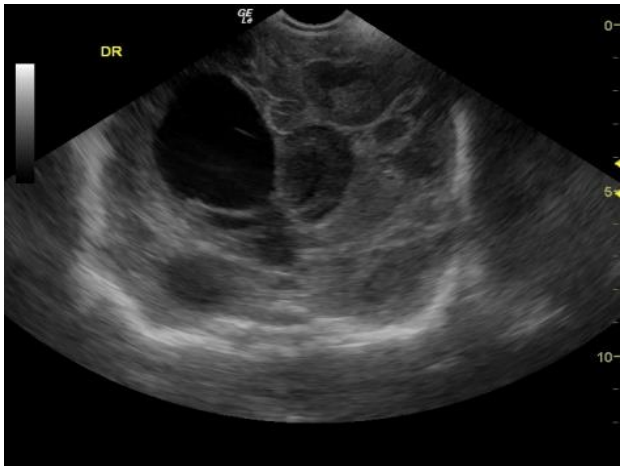

Fig. 5 – Transfontanelar ultrasound examination: bilateral hydrocephalia, bilateral disseminated porencephalic lesions and the presence of two choroid plexus cysts.

Besides these investigations, the study of the NEMO gene can prove or disprove the diagnosis; the genetic analysis of NEMO could be helpful for the rapid prenatal confirmation of the IP diagnosis and for detecting carriers, but the patients' parents refused testing (19).

Depending on the stage of the disorder, this disease must be differentiated from epidermolysis bullosa, epidermolytic hyperkeratosis, scabies, impetigo, bullous mastocytosis, varicella, herpes simplex virus infection, linear porokeratosis, acropustulosis of infancy, linear epidermal nevus, segmental vitiligo, hypomelanosis of Ito and Pallister-Killian syndrome.

The management of the patients during the neonatal period or when the vesicular stage occurs consists of applying strict hygiene measures for avoiding superinfection, but there is no specific treatment. The lesions will be kept dry and will be protected from eventual physical trauma. The vascular retinal changes are the first to progress during the first months of life, for which reason monthly perinatal screening is recommended. Xenon photocoagulation or cryotherapy promote the regression of the neovascular lesions specific for the disease. The central nervous system disorders are associated with long term negative prognosis (16)(18).

In our patients' case we have administered antibiotic therapy using Vancomycin 15 mg/kg/dose every 8 hours and Gentamycin 4 mg/kg/dose for the treatment of meningitis, anticonvulsant treatment using Diazepam 0.3 mg/kg/dose, followed by sodium valproate (Depakine) in gradually increasing dose until achieving the maintenance dose of 30 mg/kg/day as well as symptomatic and local treatment for the skin lesions. In spite of all this, the patient developed generalized porencephalic lesions in both cerebral hemispheres, with progressive alteration of the medical status and death at the age of 5 weeks.

Although the vesicle-bullae characteristic for the disease are the first ones noticed by the parents who bring the patient for a consult, they only affect the long term aesthetic prognosis. On the other hand, the ophthalmologic and psychomotor changes are serious complications that darken the prognosis of the disease (19)(20).

Case particularity

The case particularity consists of the co-existence of cutaneous features with extra-cutaneous ophthalmologic and neurologic abnormalities in a rare case of incontinentia pigmenti, as well as the fact that the neurological manifestations preceded the appearance of skin lesions.

Conclusions

Incontinentia pigmenti is a serious genetic disorder, whose prognosis depends on the presence and severity of extra-cutaneous features. The early recognition of the disease by the neonatologist, paediatrician or general practitioner and the pediatrician collaboration with the dermatologist can improve the prognosis of the disorder. The treatment most often implies interdisciplinary collaboration, the dermatologist occupying a central role in the case management. Even so, in the cases which associate neurologic and ophthalmologic abnormalities the evolution can be dreadful, in spite of sustained medical treatment.

References

1. A. Smahi. *NEMO gene: from incontinentia pigmenti to immunodeficiency*. Department de Genétique Medicale et Unité INSERM-393, Hôpital Necker, París (Francia).
2. Aradhya S, Woffendin H, Jakins T, Bardaro T, Esposito T, Smahi A, Shaw C, Levy M, Munnich A, D'Urso M, Lewis RA, Kenwrick S, Nelson DL. *A recurrent deletion in the ubiquitously expressed NEMO (IKK-gamma) gene accounts for the vast majority of incontinentia pigmenti mutations*. Hum Mol Genet. 2001 Sep 15;10(19):2171-9.
3. Alexander L. Berlin, MD, Amy S. Paller, MD, and Lawrence S. Chan, MD. *Incontinentia pigmenti: A review and update on the molecular basis of pathophysiology*. Journal of the American Academy of Dermatology, pages 169-190
4. J François. *Incontinentia pigmenti (Bloch-Sulzberger syndrome) and retinal changes*. Br J Ophthalmol. 1984 January; 68(1): 19–25. PMCID: PMC1040231
5. Jean L. Bolognia, Joseph L. Jorizzo, Ronald P Rapini. *Dermatology*. second edition. 2008, Elsevier. ISBN: 9781416029991
6. Aradhya S, Courtois G, Rajkovic A, Lewis RA, Levy M, Israël A, Nelson DL. *Atypical forms of incontinentia pigmenti in male individuals result from mutations of a cytosine tract in exon 10 of NEMO (IKK-gamma).* Am J Hum Genet. 2001 Mar;68(3):765-71. Epub 2001 Feb 8. PMCID: PMC1274488
7. Alfred White Franklin. *Incontinentia Pigmenti*. Br Med J. 1952 January 12; 1(4749): 75–77.
8. Min-Jung Song, Jong-Hee Chae, Eun-Ae Park, Chang-Seok Ki. *The Common NF-κB Essential Modulator (NEMO) Gene Rearrangement in Korean Patients with Incontinentia Pigmenti*. J Korean Med Sci. 2010 October; 25(10): 1513–1517. Published online 2010 September 20. doi: 10.3346/jkms.2010.25.10.1513
9. Nenci A, Huth M, Funteh A, Schmidt-Supprian M, Bloch W, Metzger D, Chambon P, Rajewsky K, Krieg T, Haase I, Pasparakis M. *Skin lesion development in a mouse model of incontinentia pigmenti is triggered by NEMO deficiency in epidermal keratinocytes and requires TNF signaling*. Hum Mol Genet. 2006 Feb 15;15(4):531-42. Epub 2006 Jan 6.
10. Klaus Wolff, Lowell A. Goldsmith, Stephen I. Katz, Barbara A. Gilchrest, Amy S. Paller, David J. Leffell. Fitzpatrick's Dermatology in General Medicine. Mc. Graw-Hill Professional; Seventh edition. 2007. pag. 83; 118. ISBN-10: 0071466908
11. Xiao-Ming Yin, Zheng Dong. *Essentials of Apoptosis-A Guide for Basic and Clinical Research*. 2003 Humana Press Inc, New Jersey, ISBN 1-58829-146-4
12. Jean-Baptiste S, O'Toole EA, Chen M, Guitart J, Paller A, Chan LS. *Expression of eotaxin, an eosinophil-selective chemokine, parallels eosinophil accumulation in the vesiculobullous stage of incontinentia pigmenti*. Clin Exp Immunol. 2002 Mar;127(3):470-8.
13. Kenwrick S, Woffendin H, Jakins T, Shuttleworth SG, Mayer E, Greenhalgh L, Whittaker J, Rugolotto S, Bardaro T, Esposito T, D'Urso M, Soli F, Turco A, Smahi A, Hamel-Teillac D, Lyonnet S, Bonnefont JP, Munnich A, Aradhya S, Kashork CD, Shaffer LG, Nelson DL, Levy M, Lewis RA; International IP Consortium. *Survival of male patients with incontinentia pigmenti carrying a lethal mutation can be explained by somatic mosaicism or Klinefelter syndrome*. Am J Hum Genet. 2001 Dec;69(6):1210-7. Epub 2001 Oct 22.
14. Ormerod AD, White MI, McKay E, Johnston AW. *Incontinentia pigmenti in a boy with Klinefelter's syndrome*. J Med Genet. 1987 Jul;24(7):439-41.
15. Kirchman TT, Levy ML, Lewis RA, Kanzler MH, Nelson DL, Scheuerle AE. *Gonadal mosaicism for incontinentia pigmenti in a healthy male*. J Med Genet. 1995 Nov;32(11):887-90.
16. O. Braun-Falco, G. Plewig, H. H. Wolff, W.H.C. Burgdorf . Dermatology. Second edition. Springer, pag. 1021. ISBN 3-540-59452-3.
17. W. Sterry, R. Paus, W. Burgdorf. *Dermatology*. Thieme. 2008. 10-ISBN: 3-13-135911-0 (GTV), pag. 348-349, 13-ISBN: 978-3-13-135911-7 (GTV)
18. Landy SJ, Donnai D. *Incontinentia pigmenti (Bloch-Sulzberger syndrome).* J Med Genet. 1993 Jan;30(1):53-9.
19. Osório F, Magina S, Nogueira A, Azevedo F. *Incontinentia Pigmenti with vesicular stage in utero.* Dermatol Online J. 2010 Oct 15;16(10):13.
20. Morton F. Goldberg, MD. *The Skin Is Not the Predominant Problem in Incontinentia Pigmenti*. Arch Dermatol. 2004;140(6):748-750. doi:10.1001/ archderm.140.6.748

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NEAR-INFRARED SPECTROSCOPY IN THE NEONTAL INTENSIVE CARE UNIT - A LITERATURE REVIEW

Nicoleta Ioniță[1,2*], Mirabela Adina Dima[1,2*], C Ilie[1,2], Alina Elena Agoston-Vas[2], Alexandra Nyiredi[1,2*]

Abstract

Introduction: The brain of newborns and infants is extremely vulnerable due to circulation and oxygen changes. In this concern, brain lesions occur relatively often in preterm infants. As prevention of preterm has been largely unsuccessful, it would be desirable to assess the oxygenation, haemoglobin concentration, and function of the preterm brain, in order to detect and prevent conditions, which may lead to brain lesions. Therefore one method of choice is near-infrared spectroscopy (NIRS). In 1977, Jobsis described NIRS for the first time for medical use. Several different NIRS devices are currently available: FORE-SIGHT, INVOS, NIRO, InSpectra, O2C, OM-220, OxiplexTS, TOx, and TRS-20. These devices use different near-infrared light sources (laser/LED), wavelengths, optode distances, and algorithms to calculate cerebral oxygen saturation. The INVOS and NIRO devices use spatially resolved spectroscopy.

Material and methods: The aim of this paper is to determine the clinical value of near-infrared spectroscopy in monitoring cerebral oxygenation in the NICU. A literature research on the subject was done from 1977 till date using manual library search and journal publications on Pubmed/Medline and Google scholar. Full texts including those of relevant references were collected and studied. The most relevant reported case series, case reports, and literature review were used for this study.

Results: Near-infrared spectroscopy is an optical technique based on the principle that light in the near-infrared range (700-1000 nm) is able to pass through skin, soft tissue and bone with relative ease, and can penetrate brain tissue to a depth of up to 8 cm. The light is mainly absorbed by two chromophores: hemoglobin and cytochrome aa3. NIRS measures the relative change in the tissue concentration of intravascular HbO2 and HbH. Using NIRS, we are able to infer changes in cerebral blood flow by measuring changes in the hemoglobin difference, which is obtained by calculating the difference between the changes in HbO2 and HbH concentrations.

Conclusion: In the neonatal intensive care unit (NICU) there is an acute need for a non-invasive clinical tool in order to evaluate the cerebral perfusion and possibly prevent a series of cerebral pathologies. NIRS is a safe, noninvasive, bedside technique for exploring pathophysiological mechanisms underlying brain injury in NICU patients. The most important issue regarding clinical application of NIRS monitored cerebral oxygenation and saturation is the ability to perform reliable and non-invasive long-term monitoring of cerebral oxygenation in the most immature and unstable neonates without the necessity to frequently disturb the infant.

Keywords: Near-Infrared Spectroscopy (NIRS), INVOS, Neonatal Intensive Care Unit (NICU), cerebral pulsoxymetry

Introduction

The brain remains the most poorly monitored organ in the human body, thus negative events may occur unnoticed and treatment delayed. Moreover, the brain of newborns and infants is extremely vulnerable due to circulation and oxygen changes [1]. In this concern, brain lesions occur relatively often in preterm infants. Even though, brain injury has a poor etiological background, a few postnatal factors have been associated: respiratory distress syndrome (RDS), hypocapnia due to inadvertent hyperventilation, low blood pressure (BP), perturbations in arterial and venous pressure, and low cerebral blood flow (CBF) [2].

As prevention of preterm has been largely unsuccessful, it would be desirable to assess the oxygenation, haemoglobin concentration, and function of the preterm brain, in order to detect and prevent conditions, which may lead to brain lesions. Therefore one method of choice is near-infrared spectroscopy (NIRS). NIRS has been used extensively over the past decade during cardiac and vascular surgeries to monitor oxygen delivery to the brain and spine in adults, children, and infants [7-9]. NIRS is the basis of pulse oximetry for the estimation of arterial hemoglobin saturation and in cerebral oximetry to measure regional hemoglobin saturation in the capillary beds, reflecting venous saturation.

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In 1977, Jobsis described NIRS for the first time for medical use [3], but the use in neonates to measure cerebral oxygenation was first reported by Brazy et al [4] and Delpy [5] and since then NIRS started to become more popular in neonates. Currently, NIRS is generally believed to be a valuable trend monitor in the individual patient and it is useful for comparing different groups of infants exposed to a variety of risk factors. [18-20] Several different NIRS devices are currently available: FORE-SIGHT, INVOS [Fig.1], NIRO, InSpectra, O2C, OM-220, OxiplexTS, TOx, and TRS-20 [10,11]. These devices use different near-infrared light sources (laser/LED), wavelengths, optode distances, and algorithms to calculate cerebral oxygen saturation. The INVOS and NIRO devices use spatially resolved spectroscopy.

The INVOS device measures regional cerebral tissue oxygen saturation (rSO2). These measures are thought to reflect the oxygen saturation in a mixed vascular bed dominated by venules and serve as indicators of cerebral hypoxic hypoxia.

Hypoxic-ischemic encephalopathy is a common pathophysiological condition of the newborn brain and results from disturbed oxygenation in which CBF seems to play a major role.

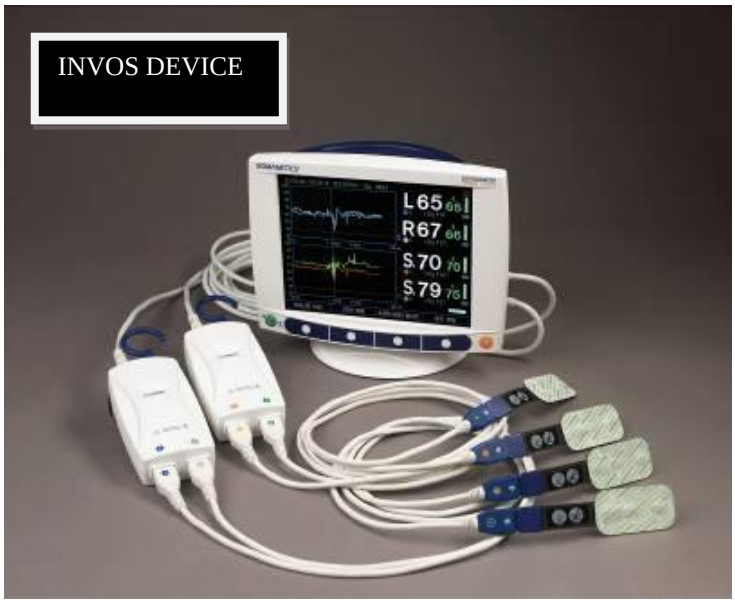

Fig.1 INVOS Device.

Purpose

In the neonatal intensive care unit (NICU) there is an acute need for a non-invasive clinical tool in order to evaluate the cerebral perfusion and possibly prevent a series of cerebral pathologies. Thus, the aim of this paper is to determine the clinical value of near-infrared spectroscopy in monitoring cerebral oxygenation in the NICU.

Material and methods

A literature research on the subject was done from 1977 till date using manual library search and journal publications on Pubmed/Medline and Google scholar. We used the following keywords: Near-Infrared Spectroscopy (NIRS), INVOS, Neonatal Intensive Care Unit (NICU), cerebral pulsoxymetry, newborn, preterm infant. Full texts including those of relevant references were collected and studied. Information relating to the NIRS technique, neonatal cerebral pulsoxymetry and NIRS utility in the NICU was extracted from the materials. The most relevant reported case series, case reports, and literature review were used for this study.

Results and discussions

General information

Near-infrared spectroscopy is an optical technique based on the principle that light in the near-infrared range (700-1000 nm) is able to pass through skin, soft tissue and bone with relative ease, and can penetrate brain tissue to a depth of up to 8 cm [12 17]. However, when illuminating the somatosensory cortex area of the premature infant, the light may enter much deeper, with signals penetrating the primary somatosensory cortex and parts of the secondary somatosensory cortex, insula, cingulate cortex, thalamus and amygdale [12].

The light is mainly absorbed by two chromophores: hemoglobin and cytochrome aa3. Their concentration and absorbance of near-infrared light in the tissue is made possible by a modified Beer-Lambert law, [6] that permits the calculation of the attenuation of a light source that passes through a given substance. When light penetrates the living tissue, part of its propagation is scattered and lost. Thus, the distance from the light source to the receiving end is affected by a differential pathlength factor (DPF). The DPF has been calculated for various biological tissues, but has also been shown to vary between participants, which may partly explain the complexity in standardizing NIRS variables across participants [17]. The hemodynamic signal obtained with the NIRS technique is based on the absorption of NIR light by hemoglobin, which in turn, depends on the oxygenation state of hemoglobin circulating through the tissues. Thus, NIRS measures the relative change in the

tissue concentration of intravascular HbO2 and HbH [12, 17].

Cerebral oxygenation and hemodynamics of human neonates through NIRS was first described by Brazy et al in 1985 and even though there have been significant advances in this field, the understanding of how blood flow, metabolism and neuronal activity interact to affect the NIRS signals remains incomplete [12]. Using NIRS, we are able to infer changes in cerebral blood flow by measuring changes in the hemoglobin difference, which is obtained by calculating the difference between the changes in HbO2 and HbH concentrations. NIRS studies can be divided into two categories: measurement of brain activity through assessment of dynamic relative changes in regional cerebral blood flow in real time; and imaging of brain activity as a function of time.

Advantages and precautions

NIRS is a safe, noninvasive, bedside technique for exploring pathophysiological mechanisms underlying brain injury in NICU patients. It has enormous potential as a tool for measuring cerebral hemodynamic responses to changes in blood pressure, oxygenation, carbon dioxide and neuronal activation. It can be adapted to many experimental and clinical situations, and combined with other electrophysiological and neuroimaging techniques [12]

However, certain treatments provided to critically ill neonates may have significant effects on cerebral circulation such as: surfactant administration, mechanical ventilation, blood transfusion, surgery, hypothermia, analgesics/sedatives, caffeine and indomethacin therapies [12, 14,15, 17].

Instrumentation – INVOS oximeter

The INVOS Oximeter system measures regional hemoglobin oxygen saturation (rSO2) of the brain in the area underlying the sensor and uses two wavelengths, 730 and 810 nm. The sensor, is applied to the forehead with an integrated medical-grade adhesive. The spatially resolved spectroscopy (SRS) method is applied by using in the sensor two source-detector distances: a 3 cm from the source and a 4 cm from the source [Fig.2]. Both sample almost equally the shallow layers in the tissue volumes directly under the light sources and detectors in the sensor, but the distant penetrates deeper into the brain. The measurement takes place in real time, providing an immediate indication of a change in the critical balance of oxygen delivery and oxygen consumption [13].

Clinical application - NICU

The most important issue regarding clinical application of NIRS monitored cerebral oxygenation and saturation is the ability to perform reliable and non-invasive long-term monitoring of cerebral oxygenation in the most immature and unstable neonates without the necessity to frequently disturb the infant [Fig.3].

Clinical conditions in NICU patients that can be investigated by NIRS technology: hypoxic hypoxia; anemic hypoxia; ischemic hypoxia; cardiovascular malformation (i.e. PDA); blood pressure passive oxygenation of the brain; artificial ventilation and effects of medication [16].

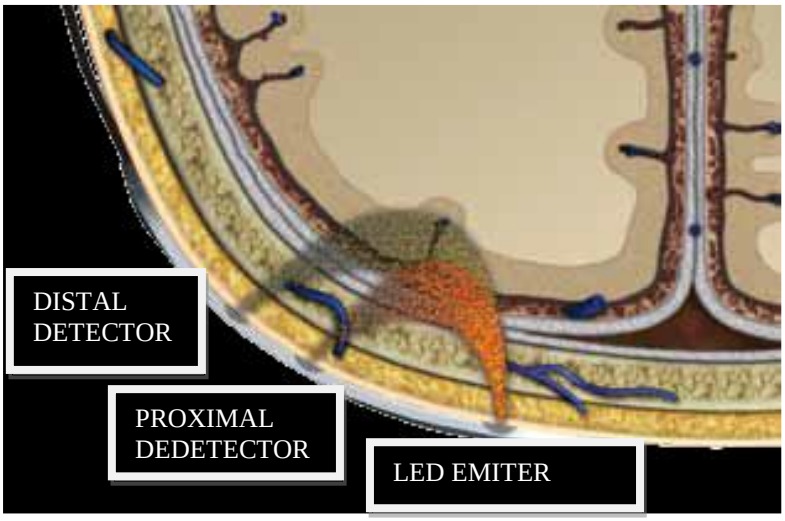

Fig. 2. Localized area of measurement.

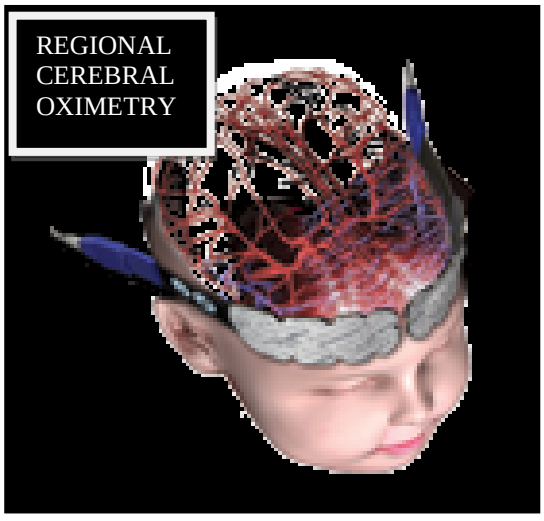

Fig. 3. Cerebral oximetry.

Conclusion

Even though great advances have been made in understanding the human brain-pathology over the past century, there are several aspects that need special attention. Some of these aspects involve the vulnerable population, the non-communicative patients, namely the neonates. NIRS has potential as a non-invasive technique for assessing cerebral structures in critically ill infants. Given the complexity of NIRS technology, the paucity of research supporting its use in critically ill infants, and the need for tight control of many confounding factors as well as artefacts, more studies are clearly needed.

References

1. Robertson DR, Justo RN, Burke CJ, Pohlner PG, Graham PL, Colditz PB. Perioperative predictors of developmental outcome following cardiac surgery in infancy. Cardiol Young. 2004; 14(4): 389–95.
2. van Bel F, den Ouden L, van de Bor M, Stijnen T, Baan J, Ruys JH. Cerebral blood-flow velocity during the first week of life of preterm infants and neurodevelopment at two years. Dev Med Child Neurol 1989, 31:320–328.
3. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977; 198(4323):1264-1267.
4. Brazy JE, Lewis DV. Changes in cerebral blood volume and cytochrome aa3 during hypertensive peaks in preterm infants. J Pediatr 1986; 108(6):983-987.
5. Delpy DT, Cope MC, Cady EB, Wyatt JS, Hamilton PA, Hope PL et al. Cerebral monitoring in newborn infants by magnetic resonance and near infrared spectroscopy. Scand J Clin Lab Invest Suppl 1987; 188:9-17.
6. Duncan A, Meek JH, Clemence M, et al. Measurement of cranial optical path length as a function of age using phase resolved near infrared spectroscopy. Pediatr Res 1996;39:889-94.
7. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Montanini S. Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery; a prospective cohort study. Eur J Anesth 2006;24:59-65.
8. Denault A, Deschamps A, Murkin J. A proposed algorithm for the intraoperative use of cerebral NIRS. Semin Cardiothorac Vasc Anesth 2007;11:274-81.
9. Edmonds HL, Ganzel BL, Austin EH. Cerebral oximetry for cardiac and vascular surgery. Semin Cardiothorac Vasc Anesth 2004;8:147-66.
10. Pellicer A, Bravo Mdel C. Near-infrared spectroscopy: a methodology-focused review. Semin Fetal Neonatal Med 2011;16(1):42-49.
11. Wolf M, Greisen G. Advances in near-infrared spectroscopy to study the brain of the preterm and term neonate. Clin Perinatol 2009;36(4):807-834.
12. Bartocci M. Brain functional near infrared spectroscopy in human infants. Karolinska Institutet. Stockholm: Karolinska University Press, 2006
13. www.somanetics.com
14. Lemmers PM, Toet MC, van Bel F. Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants. Pediatrics 2008;121(1):142-147.
15. van Alfen-van der Velden AA, Hopman JC, Klaessens JH, Feuth T, Sengers RC, Liem KD. Effects of midazolam and morphine on cerebral oxygenation and hemodynamics in ventilated premature infants. Biol Neonate 2006;90:197-202.
16. Naulaers G, Caicedo A, van Huffel S. Use of Near-Infrared Spectroscopy in the Neonatal Intensive Care Unit. Neonatal Monitoring Technologies: Design for Integrated Solutions. IGI Global, 2012. 56-83. Web. 4 Nov. 2013. doi:10.4018/978-1-4666-0975-4.ch004
17. Wolfberg AJ, du Plessis AJ. Near-infrared spectroscopy in the fetus and neonate. Clin Perinatol 2006; 33:707-28.
18. Roche-Labarbe N, Carp SA, Surova A, Patel M, Boas DA, Grant PE, Franceschini MA. Noninvasive optical measures of CBV, StO2, CBF index, and rCMRO2 in human premature neonates' brains in the first six weeks of life. Hum Brain Mapp 2010;31(3):341-352.
19. Vanderhaegen J, Vanhaesebrouck S, Vanhole C, Casaer P, Naulaers G. The effect of glycaemia on the cerebral oxygenation in very low birthweight infants as measured by near-infrared spectroscopy. Adv Exp Med Biol 2010;662(5):461-466.
20. Yoxall CW, Weindling AM. Measurement of cerebral oxygen consumption in the human neonate using near infrared spectroscopy: cerebral oxygen consumption increases with advancing gestational age. Pediatr Res 1998;44(3):283-290.

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NEONATAL ASPECTS REGARDING NEWBORNS RESULTED FROM MOTHERS WITH PREGNANCY-INDUCED HYPERTENSION

Rodica Ilie[1], C Ilie[2], M Craina[2], Daniela Iacob[2], Alexandra Nyiredi[2], C Angelescu[2]

Abstract

Introduction The paper addresses from the neonatologist clinician's perspective to a category of high risk newborns, affected by pregnancy-induced hypertension, a pathological entity particular only in gestational period. It is different from pre-existing hypertension before pregnancy and disappears after childbirth and delivery of the placenta.

Material and method Based on rigorous inclusion and exclusion criteria, were established two equal groups of newborns (n=116): a study group including newborns of mothers with pregnancy-induced hypertension and a study group including newborns whose mothers have not pregnancy-induced hypertension, randomized case-control pattern. There were analyzed for comparison a number of 18 parameters, focused on their postnatal development issues. For their registration it was used the database from Neonatology Clinic "Bega" Timisoara. For statistical data processing we used SPSS 17.0.

Results Significant results were considered those who presented major differences in adaptation and neonatal pathology, the group study being affected. For a confidence interval of 95%, we recorded $p < 0,05$ (significant differences), for next parameters: low birth weight, the degree of immaturity, early neonatal adapting difficulties, the need of neonatal reanimation and mechanical ventilation in the first 24 hours of life and the incidence of neonatal hypoxic pathology.

Conclusions By reducing placental blood flow, pregnancy-induced hypertension significantly affect fetal nutrition and oxygenation with whole metabolic consequences. This is more important when the onset is in early pregnancy and the duration of fetal suffering is more prolonged. This category is represented by neonates of mothers who developed pregnancy-induced hypertension.

Keywords: newborn, pregnancy-induced hypertension

Introduction

Pregnancy-induced hypertension, with all its forms and complications represents *a crossroad* where there are meeting concerns of the obstetrician, cardiologist, neonatologist, and not least the pathologist because the disease's morphological substrate is given by the placental vascular lesions, or more precisely by *I.M.F lesion with damage of the placental homeostatic unity.* The strongest argument of the morphological substrate is that *the disease occurs only in pregnant women, so in the presence of the placenta and disappears after childbirth and delivery of the placenta.* We are talking about pregnancy-induced hypertension only in pregnant women who did not have hypertension before pregnancy [1, 2].

As a matter of the human species pathology, *the disease does not benefit of models, research and experimental results.*

Major fetal consequences of the disease are dependent on the age of onset, intensity and duration of aggression and therapeutic control of the disease. There are two major fetal consequences [3, 4, 5]:

- *Chronic fetal hypoxia*, resulting in deterioration of gas exchange in the maternal-fetal interface;
- *Fetal malnutrition* as a result of maternal-fetal alteration of food intake at the same level with the exchange surface.

Pregnancy-induced hypertension has a significantly influence on the fetal prognosis and can lead to various degrees of fetal distress or even death of the fetus in the womb. Equally signifiant affects the disease the prognosis of premature newborns, intrauterine growth restriction (limitation), early neonatal adapting difficulties or severe neonatal pathology with sustainable neurological sequelae (cerebral palsy) [6, 7, 8].

Materials and methods

The study was conducted at the Clinic of Obstetrics-Gynecology and Neonatology of the Emergency County Hospital Timisoara. To achieve the study group there have been used criteria to answer the study objectives in the clinical-research stage and criteria to allow the selection of the casework required for pathological research of the placenta.

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Inclusion criteria: **g**estational age ≥ 28 weeks, birth weight ≥ 1000 g, mother with pregnancy-induced hypertension without complications, single pregnancy, neonatal favorable evolution, with discharge to home.

Exclusion criteria: GA <28 weeks, BW<1000 g, twins, death in the neonatal period, serious associated pathology (infection, congenital malformations, perinatal asphyxia), mother with complications of pregnancy-induced hypertension.

The study group included 116 infants of mothers with pregnancy-induced hypertension over a period of 4 years (2008-2011).

Compared to the total number of births during the study (n = 9664) the incidence of pregnancy-induced hypertension was 1.26%.

For comparison was formed a group of newborns whose mothers have not pregnancy-induced hypertension *(randomized case - control pattern).*

There were analyzed for comparison a number of 18 items,which focused on physical and maturity parameters of the newborn as well as adaptation issues and their neonatal hypoxic pathology.

Equal groups were formed, the database is built in an Excel file by sequential entering of the following documents data (observation sheet) of each patient.

The statistical study of the data was performed using SPSS 17.0.

The parameters taken in the study were:

- Sex of newborns
- Gestational age at birth (weeks of amenorrhea)
- Birth weight (g)
- The size at birth (cm)
- Head circumference at birth (cm)
- Pathological labor
- Pathological presentation
- The way of birth (naturally or by caesarean section)
- 1-minute Apgar score
- The need for reanimation and intensive care at birth
- Mechanical ventilation in the first 24 hours of life
- Duration of hospitalization (days)
- Initial Nutrition
- Hypoxic neonatal pathology (Sarnat classification).

Results and discussion

The parameters considered in the study were analyzed comparatively parameter by parameter between the study group and the control group. Significant differences were registered in terms of physical parameters at birth between the study group and control group.

For the birth weight (Fig.1) there has been a highly significant difference between the cases of the study group and the cases of the control group.Regarding the degree of maturity there has been a significant difference between the study group and the control group in the incidence of prematurity (Fig. 2). Most cases presented, along with the immaturities caused by prematurity and the fetal hypoxic suffering more or less prolonged, also intrauterine growth restriction from moderate to severe.

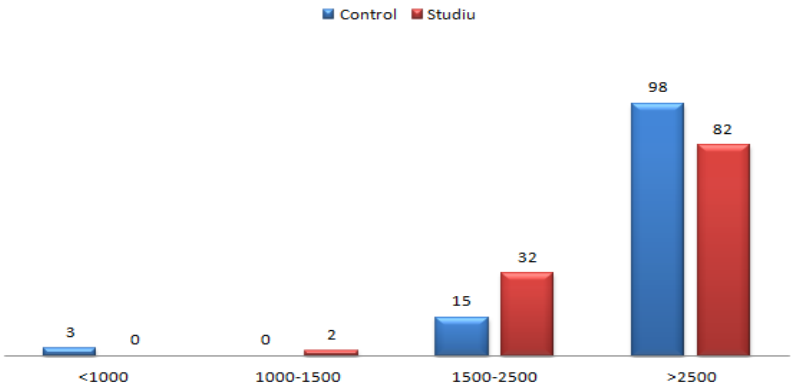

Fig.1. Distribution of cases according to birth weight (g).

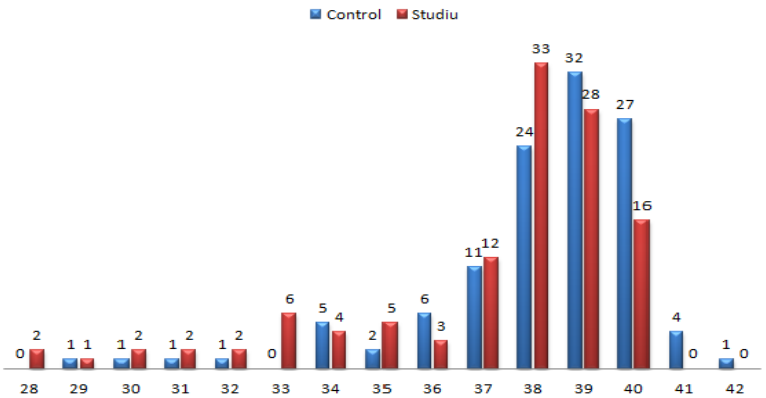

Figure 2. Distribution of cases according to gestational age (weeks of amenorrhea).

The data presented and illustrated record a major impact of hypertension induced by pregnancy on the fetal growth and development, with considerable damage in fetal weight with a mean difference of this parameter above 300 grams between the two groups. Also, the cases with early onset disease and poor outcome of the disease imposed challenge of premature birth in order to remove the fetus from adverse intrauterine environment and prevent fetal death in utero.

The degree of chronic suffering with intrauterine growth restriction and preterm birth significantly more frequent in the study group influenced the other parameters such as neonatal adapting (Apgar score), the need to reanimate at birth and the need for mechanical ventilation in the first 24 hours of life.

The clinical data have been focused on neonatal hypoxic pathologies, whose incidence was significantly higher in the cases of the study group vs the control group (Fig. 3).

The diagnosis of neonatal hypoxic suffering was based on clinical data included in the *quoted Sarnat* (Table 1), on the neurological exam of the newborn and its future evolution. On this basis they could classify the neonates with hypoxic events in mild, moderate and severe, observing *the tenth revision of the International Classification of Diseases WHO.*

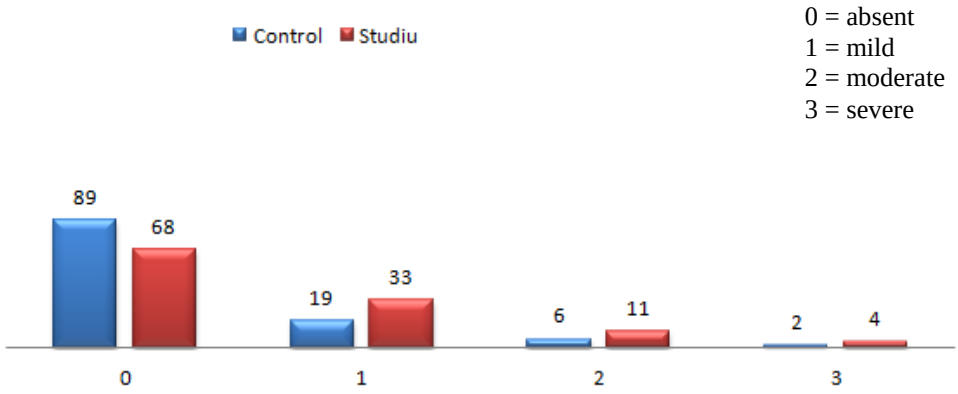

Fig.3. Distribution of cases according to the incidence of hypoxic pathology in the neonatal period.

Table 1. Sarnat Score Sheet.

Variable	**Stage I**	**Stage II**	**Stage III**
Level of Consciousness	Alert	Lethargic	Coma
Muscle Tonus	Normal/hipertonic	Hipotonic	Flaccid
Reflexes	Increase	Increase	Descreased/absent
Myoclonus	Present	Present	Absent
Seizures	Absent	Frequent	Frequent
Complex Reflexes			
• Suck	Activ	Weak	Absent
• Moro (startle)	Exaggerated	Incomplete	Absent
• Grab	Normal/Exaggerated	Exaggerated	Absent
• Tonic Neck	Normal	Overactiv	Reduced/absent
Automatic Function			
• Pupils	Mydriasis, reactive	Miosis, reactive	Variable/fixed
• Respirations	Regular	Variable in number and depth, periodic	Ataxic, apneic
• Heart Rate	Normal/Tahicardic	Bradicardic	Bradicardic

The other parameters studied were not significantly different between the study group vs the cases in the control group.

In Tables 2 and 3 are shown in summary parameters significantly different from the study group and control group, that can be correlated with the impact of pregnancy-induced hypertension on the placental and fetal complex in the prenatal period.

Pregnancy-induced hypertension is defined as an increase of blood pressure over the values of 140/90 mmHg, or more precisely an increase of 30 mmHg systolic or 15 mmHg diastolic blood pressure over the core values of the

pregnant woman. Correct definition is necessary because the disease is often called preeclampsia [9,10]. Preeclampsia is a pregnancy-induced hypertension very early onset (after 20 weeks of gestation) with proteinuria or edema. It is widely accepted that early onset pregnancy-induced hypertension has a major impact on maternal-fetal circulation unknown or uncontrolled can develop into complications. The disease can develop into two major complications [10, 11, 12]:

- Eclampsia – which involves seizures that are not related to a neurological condition, to a pregnant woman which meets the criteria of preeclampsia.
- HELLP syndrome associating three biological disorder: Hemolysis, Elevated Liver enzymes, and Low Platelets.

Reduced placental circulation and blood flow is the main cause maternal-fetal nutrient supply reduction. If onset occurs early in the fetal period (after 20-22 weeks of gestation) and duration (with or without treatment) is prolonged, fetal harm will be severe and often requires its removal by caesarean section, even if it is extreme immaturity. Along with severe malnutrition, in this case the fetus is affected by hypoxemia / severe hypoxia with risk of fetal death. If onset is late (after 28-30 weeks of gestation), fetal maturity is better and hence the tolerance to hypoxia and malnutrition [13, 14, 15].

When the fetus stops growing, in general, it also starts to unfold the impact of fetal hypoxia, but this time is difficult to diagnose. For these reasons a pregnancy complicated with pregnancy-induced hypertension requires frequent monitoring to capture the moment [14,15].

Table 2 Distribution of the average and standard deviations for the parameters studied in the study group vs the control group.

PIH

	Parameters	S. G.		C. G.		Comments
		M	DS	M	DS	
1	GA (weeks)	37,22	2,77	38,20	2,18	P = 0,0032
2	BW (g)	2829,57	571,57	3102,72	700,46	P = 0,0011
3	Length at birth(cm)	49,03	3,39	50,41	3,43	P = 0,0024
4	CP at birth (cm)	32,73	1,91	33,42	2,10	P = 0,0095
5	APGAR score at 1 minute	8,49	1,31	9,00	1,27	P = 0,0030
6	Length of hospital stay(days)	5,68	3,73	5,17	3,10	P = 0,260

Table 3. The numerical and the percentage distribution of the parameters studied in the study group vs in the control group.

PIH

	Parameters	S. G.		C. G.		Comments
		Nr	%	Nr	%	
1	Resuscitation at birth and TIN	21	18,10	13	11,20	P = 0,194
2	Mechanical ventilation in the first 24 hours	15	12,93	3	2,58	P = 0,0069
3	Hypoxic neonatal pathology (Sarnat criteria)	48	41,37	19	16,37	P = 0,041

Conclusions

1. Pregnancy-induced hypertension is a pathological condition affecting the morbidity, mortality and the newborn outcome. In relation to the total number of births during the study (n = 7654), the incidence of the disease was 1.76%.
2. The study conducted on a group of infants of mothers with pregnancy-induced hypertension (n = 116 cases) compared with a equal group of newborns coming from mothers without pregnancy-induced hypertension has recorded the following significant issues:
   - a significant difference in growth parameters (W, L, CP) and the degree of immaturity among the study group vs the control group;
   -an average weight difference of over 300 g between the 2 groups were significantly due to intrauterine growth restriction in the study group, regardless of gestational age;
3. a significantly higher incidence of the need for neonatal intensive care measures and their continuing in the neonatal intensive care unit in the cases of the study group; the hypoxic neonatal pathology and the the respiratory pathology was determined, and the incidence of cases of the study group was highly significant compared to the control group.The degree of fetal immaturity and / or intrauterine growth restriction vs. "the necessity" of pregnancy ending remains one of the most controversial issues of

perinatal medicine: a good obstetrician-neonatologist cooperation is the key to choosing the best solution for "fetal welfare."

4. Improving the fetal prognosis can be achieved only through a careful maternal and fetal monitoring individualized treatment in hospital conditions and allows the optimal timing of birth and birth path.
5. In addition to these research methods the substrate generating perinatal fetal distress, I believe that taking and researching the placenta can provide the key to elucidate this problem and plausible explanations for a possible adverse outcome of these cases.

References

1. L. K. Wagner, "Diagnosis and management of preeclampsia," American Family Physician, vol. 70, no. 12, pp. 2317–2324, 2004.
2. Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. Am J Epidemiol 2002;155:203–9
3. R. A. Ødegård, L. J. Vatten, S. T. Nilsen, K. A. Salvesen, and R. Austgulen, "Preeclampsia and fetal growth," Obstetrics and Gynecology, vol. 96, no. 6, pp. 950–955, 2000.
4. D. M. Shah, J. P. Shenai, and W. K. Vaughn, "Neonatal outcome of premature infants of mothers with preeclampsia," Journal of Perinatology, vol. 15, no. 4, pp. 264–267, 1995
5. B. M. Sibai, "Preeclampsia as a cause of preterm and late preterm (near-term) births," Seminars in Perinatology, vol. 30, no. 1, pp. 16–19, 2006
6. P. H. Gray, M. J. O'Callaghan, H. A. Mohay, Y. R. Burns, and J. F. King, "Maternal hypertension and neurodevelopmental outcome in very preterm infants," Archives of Disease in Childhood: Fetal and Neonatal Edition, vol. 79, no. 2, pp. F88–F93, 1998
7. S. W. Cheng, H. C. Chou, K. I. Tsou, LI. J. Fang, and PO. N. Tsao, "Delivery before 32 weeks of gestation for maternal pre-eclampsia: neonatal outcome and 2-year developmental outcome,"Early Human Development, vol. 76, no. 1, pp. 39–46, 2004
8. C. S. Wu, E. A. Nohr, B. H. Bech, M. Vestergaard, J. M. Catov, and J. Olsen, "Health of children born to mothers who had preeclampsia: a population-based cohort study," American Journal of Obstetrics and Gynecology, vol. 201, no. 3, pp. 269-e1–269-e10, 2009
9. L. L. Simpson, "Maternal medical disease: risk of antepartum fetal death," Seminars in Perinatology, vol. 26, no. 1, pp. 42–50, 2002
10. ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002," Obstetrics & Gynecology, vol. 99, no. 1, pp. 159–167, 2002.
11. B. Haddad and B. M. Sibai, "Expectant management of severe preeclampsia: proper candidates and pregnancy outcome," Clinical Obstetrics and Gynecology, vol. 48, no. 2, pp. 430–440, 2005
12. J. R. Barton, J. M. O'Brien, N. K. Bergauer, D. L. Jacques, and B. M. Sibai, "Mild gestational hypertension remote from term: progression and outcome," American Journal of Obstetrics and Gynecology, vol. 184, no. 5, pp. 979–983, 2001
13. M. Habli, R. J. Levine, C. Qian, and B. Sibai, "Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation," American Journal of Obstetrics and Gynecology, vol. 197, no. 4, pp. 406 e1–406 e7, 2007
14. Sivakumar S, Bhat BV, Badhe BA., " Effect of pregnancy induced hypertension on mothers and their babies", Indian J Pediatr. 2007 Jul;74(7):623-5.
15. Piper JM; Langer O; Xenakis EM; McFarland M; Elliott BD; Berkus MD . Perinatal outcome in growth-restricted fetuses: do hypertensive and normotensive pregnancies differ? Obstet Gynecol 1996; 88:194-9

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ERRATUM

Erratum to JURNALUL PEDIATRULUI – Year XVI, Vol. XVI, Nr. 63, july-september 2013

- Pp 27, line 2, *Mihai Gafencu[1], Iulia Simina Jurca[1], Laura Leahu[1], Andra Mitoceanu[1], Otilia Marginean[2], Gabriela Doroș[1], Bogdan Korbuly3[1]* must be replaced with: *Mihai Gafencu[1], Iulia Simina Jurca[1], Laura Leahu[1], Andra Mitoceanu[1], Otilia Marginean[2], Bogdan Korbuly[1], Gabriela Doroș[1]*
- Pp 31, line 41, *Correspondance to: Mihai Gafencu and Jurca-Simina Iulia, Iosif Nemoianu Street, no. 2, 300011, Timisoara, Romania E-mail: mgafencu@umft.ro, jurca.iulia@gmail.com* must be replaced with: *Correspondance to: Gabriela Doroș, Iosif Nemoianu Street, no. 2, 300011, Timisoara, Romania E-mail: gdoros@gmail.ro*

MANUSCRIPT REQUIREMENTS

The manuscript must be in English, typed single space, one column on A4 paper, with margins: top – 3 cm, bottom – 2,26 cm, left – 1,5 cm, right – 1,7cm. A 10-point font Times New Roman is required.

The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, and first author's correspondence address.