GEORGE EMIL PALADE "UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY OF TÂRGU MUREŞ"

DOCTORAL SCHOOL OF MEDICINE AND PHARMACY

ABSTRACT OF PhD THESIS

Early diagnosis of psychomotor development delay in pediatric patients with congenital heart defects after cardiovascular surgery

PhD student: Dr. Pop (Chiperi) Lăcrămioara-Eliza

Scientific coordinator: Conf. Univ. Dr. Muntean Iolanda

TÂRGU MUREŞ 2024

Background: Congenital heart defects (CHD) are the most common congenital malformations in pediatric pathology, and impaired psychomotor development is the most common comorbidity in CHD patients. Psychomotor delay was detected both in patients with cyanogenic CHD (reduced cerebral oxygenation) and in those with non-cyanogenic CHD (adequate cerebral oxygenation). Patients with psychomotor development problems should be identified and treated as early as possible, because early treatment is much more effective and less expensive compared to late intervention.

Purpose: The purpose of the research was to establish the early diagnosis of delayed psychomotor development in patients with CHD, to detect the factors that influence it and the impact on the quality of life.

Methodology: Studies were conducted on a group of 79 patients. The inclusion criteria were: pediatric patients with CHD who were to undergo cardiovascular surgery, with various types of CHD (tetralogy of Fallot as a prototype of cyanogenic CHD and ventricular septal defect as a prototype of non-cyanogenic CHD) aged between 0-6 years. The exclusion criteria were represented by pathologies that affect psychomotor development: prematurity, genetic syndromes, other congenital malformations, the need for postoperative ECMO or several cardiovascular surgeries. The patients were divided into two groups based on the peripheral blood oxygen saturation: cyanotic group <95% (CG) and non-cyanotic group >=95% (NCG). The assessment of psychomotor development was carried out by the Denver Development Screening Test II (DDSTII) in 4 domains (personal-social, fine motor, language, gross motor). Blood samples were collected for neuromarker dosing. During surgery, regional brain tissue oxygen saturation was monitored using near-infrared spectroscopy (NIRS).

Study 1 Neuromarkers that can predict impaired psychomotor development in children with CHD after cardiac surgery—a systematic literature review: The aim of this review was to evaluate data on neuromarkers used to assess the impact of cardiovascular surgery on psychomotor development in children with CHD. A systematic search was performed in the PubMed and Google Scholar databases. Of the 713 publications reviewed, 10 studies (471 patients) met the inclusion criteria. Data related to patients (age, CHD), neuroimaging before and after surgery, assessment of psychomotor development, and follow-up period were evaluated. Results were reported according to PRISMA guidelines. Conclusions include: neuron-specific enolase (NSE) and brain-derived neurotrophic factor (BDNF) are not reliable neuromarkers, conflicting results have been reported for protein S100B (pS100), little evidence for activin A, but glial fibrillary acidic protein (GFAP) could represent a reliable neuromarker for acute brain injuries after surgery.

Study 2 Epidemiology of psychomotor developmental delay in pediatric patients with CHD
Introduction: The aim of this study was to evaluate the psychomotor performance of patients with CHD before the institution of treatment (interventional, surgical). **Methods**: It was a prospective study that included children with no detectable neurological deficit on clinical examination. **Results:** The psychomotor development of 77 patients evaluated by DDSTII revealed delay in 97% in the CG and in 54% in the NCG (p=0.03). The most affected domains were gross motor and personal-social. Overall developmental and functional scores were lower in the CG. Factors that correlated with psychomotor development were prenatal diagnosis (p=0.012) and breastfeeding (p=0.008). **Conclusions:** Delay in psychomotor development was detected in a high percentage of children with unoperated CHD, with lower developmental scores in CG, correlating with prenatal diagnosis and breastfeeding.

Study 3 Neuromarkers that could predict impaired psychomotor development in children with CHD before surgery - brain-derived neurotrophic factor as a promising neuromarker
Introduction: The aim of the study was to evaluate the predictive value of neuromarkers for psychomotor impairment in pediatric patients with CHD, before treatment (interventional or surgical). **Methods:** A prospective study was conducted. Analysed neuromarkers were: NSE, pS100, BDNF and GFAP. **Results:** 77 children with no clinically detectable developmental deficits were included. After evaluating them by DDSTII, correlation between the type of CHD and psychomotor impairment (p<0.0001, RR=2.604, CI=2.07-3.26) was observed. The values of NSE and BDNF were higher in the CG, respectively, pS100 and GFAP had slightly higher values in the NCG. BDNF was positively correlated with psychomotor development (r=0.35, p=0.023) with an AUC of 0.72 in the ROC analysis with a cut-off of 5895 pg/ml. **Conclusion**: A moderate positive correlation was found between psychomotor development and levels of BDNF. BDNF showed moderate discrimination ability in predicting psychomotor developmental outcomes.

Study 4 The diagnostic and prognostic role of serum markers of cerebral dysfunction in children with CHD undergoing cardiovascular surgery
Introduction: The objectives of this study were to evaluate the role of neuromarkers in the diagnosis of acute brain injuries and as prognostic markers for the impairment of psychomotor development in the short term after surgical intervention. **Methods**: Pediatric patients with CHD undergoing elective cardiac surgery, evaluated by DDSTII preoperatively and 4-6 months postoperatively, were included. Blood samples were collected preoperatively and postoperatively. Neuromarkers analysed were GFAP, BDNF, pS100 and NSE. **Results**: Forty-two patients were included in the study. In the CG, a good diagnostic model was observed between NIRS and GFAP values (AUC=0.7) and a good predictive model was observed for GFAP and developmental scores (AUC=0.667). A correlation was found between NSE and developmental quotient scores (r=0.09;p=0.046). **Conclusions**: Among the studied neuromarkers, GFAP proved to be

a good diagnostic and prognostic marker in patients with cyanotic CHD, ENS having only prognostic value.

Study 5 Diagnostic and prognostic role of glial fibrillary acidic protein in the dynamics of psychomotor development in patients with CHD requiring cardiovascular surgery

Introduction: The aim of this study was to evaluate GFAP as a marker of short-term psychomotor developmental delay in pediatric patients with CHD after cardiovascular surgery. **Methods:** Included patients were assessed using the DDSTII before and then 4-6 months after surgery. Blood samples were collected preoperatively and postoperatively. **Results**: Postoperative, GFAP had significantly higher values (p=0.0248) in the CG that correlated with psychomotor development delay (p=0.01). The association between GFAP and NIRS was analyzed and significant differences were found in both groups, with a good predictive model in the NCG (AUC=0.7). **Conclusions:** PFAG could be a reliable neuromarker in the identification of early acute brain injury documented by NIRS monitoring in the perioperative period and could also identify short term impairment of psychomotor development, postoperatively.

Study 6 Tau protein and myelin basic protein in pediatric CHD patients undergoing cardiac surgery: preliminary evaluation as novel neuromarkers of brain injury

Introduction: The aim of this study was to evaluate two new neuromarkers, myelin basic protein (MBP) and Tau protein (pTau) as diagnostic and/or prognostic markers for perioperative brain injury in CHD patients. **Methods:** Forty patients were included and evaluated by DDSTII. Blood samples were collected preoperatively and postoperatively. **Results:** Neuromarker values were increased postoperatively, with a statistical significance reached only in the NCG ($p<0.0001$). A significant positive correlation was observed between preoperative MBP and patients' albumin, hemoglobin, height, and weight. In association with cerebral saturations, an acceptable predictive model was observed with pTau in the cyanotic group (AUC=0.7). **Conclusion**: Increased postoperative concentrations of pTau and MBP were observed in both groups. Increased pTau values were associated with perioperative hypoxemia.

Study 7 Evaluation of the impact of caring for a child with CHD on the mother's quality of life

Introduction: The mother's quality of life is a surrogate for the child's quality of life when he is too young to be evaluated himself. The aim of this study was to assess the impact that caring for a child with CHD has on the mother's quality of life and to detect whether there is any improvement after surgical correction of her child's heart defect. **Methods:** A prospective study was conducted that included mothers of children with CHD hospitalized for surgical correction. To objectively quantify the mothers' quality of life, they were evaluated by Impact of a Child with Congenital Anomaly on Parents (ICCAP) questionnaire that assesses 6 domains applied before surgery and at two later times (4-6 months and 10-14 months) after the surgical correction of their child's CHD. **Results**: 79 mothers were evaluated. An overall score was calculated for each domain of the ICCAP questionnaire at each assessment and the scores were compared with each other. The contact with caregivers domain had a higher score at the third evaluation ($p=0.02$). Lower scores were observved in mood domain($p<0.0001$) and fear and anxiety domain ($p<0.0001$) at the third assessment. **Conclusions**: The ICCAP questionnaire identifies areas where mothers are at risk and need intervention to achieve a better quality of life for themselves and their children. An improvement in mother's quality of life after surgical correction of their child's MCC was demonstrated.

Originality of the thesis: Psychomotor impairment is an important concern in the development of patients with CHD and in Romania, there are so far no reported data on this subject. There are no pre- or post-operative psychomotor screening recommendations, although the number of patients with psychomotor development delay is overwhelming, as it emerged from this study. Patients were included from the case file of the Emergency Institute for Cardiovascular Diseases and Transplantation in Târgu Mureș. Due to the high specialization of this center in the diagnosis and treatment of patients with CHD as well as it's addressability from all regions of the country, it can be stated that the epidemiological data of the included patients reflect the characteristics of patients from the whole of Romania. A number of neuromarkers (GFAP, BDNF, pS100 and NSE) were studied with the aim of detecting a suitable marker for the diagnosis and/or prognosis of brain damage in patients with CHD. Preoperatively, the BDNF has been shown to exhibit moderate discriminative ability to predict psychomotor developmental outcomes. Postoperatively, GFAP proved to be a relevant neuromarker for the diagnosis of postoperative brain lesions and the prediction of psychomotor development in patients with cyanotic CHD. The present work also evaluated two new neuromarkers, not previously used in pediatric studies, MBP and pTau. Elevated pTau values have been shown to be associated with perioperative cerebral hypoxemia. The mother's quality of life is a surrogate that can approximate the child's quality of life when the child is too young to be assessed himself, because the mother has a crucial role in the child's development. Ensuring a good quality of life for a mother is essential for the healthy and happy development of the child. The ICCAP questionnaire identifies areas where mothers are at risk and need intervention to improve the quality of life for themselves and their children. The study demonstrated an improvement in mothers' quality of life after surgical correction of their child's CHD.